Hosp. Lib.

The Journal of Pediatrics

VOL. 8 JANUARY, 1936 No. 1

Original Communications

NORMAL CEVITAMIC (ASCORBIC) ACID DETERMINATIONS IN BLOOD PLASMA AND THEIR RELATIONSHIP TO CAPILLARY RESISTANCE

ARTHUR F. ABT, M.D., CHESTER J. FARMER, AND I. M. EPSTEIN, M.D.
CHICAGO, ILL.

IN A RECENT paper[1] on the treatment of infantile scurvy with cevitamic (ascorbic) acid we published the first determinations of the cevitamic acid content of the blood serum in this condition. In a second publication[2] we have reported a method for the determination of the reduced portion of cevitamic acid in small amounts of blood. With the perfection of the method we are now enabled to report values for the reduced blood cevitamic acid in the blood of normal infants and children. In conjunction with these studies we have employed a machine and method for determining by suction the capillary skin resistance as described by Cutter and Johnson.[3] In addition to the values obtained from normal infants and children, we have also observed a certain number of individuals showing subnormal values, and this group we feel justified in calling examples of subclinical scurvy.

DESCRIPTION OF METHOD FOR DETERMINING THE REDUCED CEVITAMIC ACID CONTENT OF BLOOD PLASMA

Five or more cubic centimeters of blood are withdrawn from a vein and immediately oxalated in a test tube. The blood plasma is deproteinized by the tungstic acid method of Folin, and the filtrate thus obtained is titrated against sodium 2:6 dichlorobenzenoncindophenol, by which titration the cevitamic acid content (reduced form) may easily be computed. The use of the tungstic acid filtrate allowed us to obtain a satisfactory and accurate end-point. The end-point with trichloracetic acid filtrates, which we had used previously in blood from our scurvy patients, was not

From the Departments of Pediatrics and Chemistry, Northwestern University Medical School.

The investigation was aided by a grant from Merck and Company, Rahway, New Jersey.

sharp, and the results thus obtained were high. In using the tungstic acid filtrates we measure only the cevitamic acid present in the reduced state. However, as far as we have been able to determine, the cevitamic acid content of blood thus measured accurately indicates the nutritional state of the body relative to vitamin C.

REVIEW OF PREVIOUS DETERMINATIONS OF ASCORBIC ACID CONTENT OF BLOOD SERUM

In our first report,[1] using trichloracetic acid to deproteinize the blood serum and 2:6 dichlorobenzenoneindophenol as indicator, we pointed out in two cases of infantile scurvy that the reduced cevitamic acid in the blood serum was extremely low in this condition and was definitely increased following oral feeding of cevitamic acid. We also noted that the values which we reported were probably too high, and further studies have convinced us that this was so.

There are only a few references in the literature on the determination of the cevitamic acid content of the blood serum. E. Gabbe[4] determined the total cevitamic acid content of the blood serum in a number of adult patients suffering from various illnesses. His values ranged from 0.14 to 1.21 mg. per cent. Gabbe believed that the differences could be explained from the varying intake of vitamin C-containing foods in the diet of his patients.

Mirsky, Swadesh, and Soskin[5] determined the total ascorbic acid content of the blood of normal and pathologic patients. Their values for normal individuals ranged from 1.19 to 2.66 mg. per cent, and their values for patients suffering with chronic diseases from 1.11 to 2.88 mg. per cent. These authors were unable to make any correlation for the values of cevitamic acid which they found in the blood and the dietary regime.

In none of the reports which have come to our attention have we been able to find normal or pathologic values for infants and children.

METHOD OF DETERMINING CAPILLARY SKIN RESISTANCE

We have employed the instrument described by Cutter and Johnson[3] for measuring the capillary resistance. The instrument consists of a large aneroid manometer for measuring negative pressure, graduated from 0 to 750 mm. of mercury and also from 750 to 0 mm. of mercury barometric pressure. There is also a mercury manometer for checking the accuracy of the aneroid gauge. This gauge system is connected to a reservoir of 500 c.c. capacity, and this in turn is connected with a small, motor-driven, oil-sealed suction pump capable of reducing the pressure to within 0.25 mm. of mercury. There are two bipass needle valves by which air can be admitted into the system, and the desired degree of vacuum may thus be obtained and held. The reservoir is connected by means of a heavy rubber tube to a small glass suction cup which is applied to that region of the skin which is to be tested. A 5 mm. aperture is situated on the lower surface of the suction cup, which is applied to the skin. The upper surface of the cup is flat so that the skin area under observation may be visualized while the measurement is being made, and the appearance of hemorrhage can thus be noted with the naked eye or with the aid of a lens. We have found that an electric otoscope will aid in illuminating the

skin area as well as furnishing an adequate lens. Attached to the suction cup is a stopcock which permits shutting off the cup from the rest of the system so that the pressure may be regulated before suction on the skin is begun.

The instrument is compactly enclosed in a carrying case which allows for easy transportation. In operating the instrument the electric suction pump is turned on with the stopcock of the suction cup closed. When the desired negative pressure is reached on the gauge by adjusting the needle valve regulators, the cup is applied to the skin and the stopcock is opened. Suction is applied for thirty seconds. The stopcock is then closed; the cup is removed from the skin; and hemorrhages over the area of suction are counted and recorded. Readings are made at 50 mm. differences of negative pressure. Small bright red hemorrhages have been interpreted as capillary ruptures. Diffuse redness has been thought to be due to hemorrhage by diapedesis. We have recorded the hemorrhages occurring peripherally separately from those occurring centrally in the field of skin examined, as we felt that the former might be influenced by trauma from the edge of the suction aperture. We considered three or more central hemorrhages in the skin area tested at a given pressure as evidence of capillary rupture at that pressure. The 5 mm. aperture causes no pain or discomfort in infants and children, which might be the case if an aperture of larger diameter were employed. The area of skin thus examined is adequate for the readings and is small enough so that when hourly or daily measurements are made, a sufficient skin area in a given region is available.

REVIEW OF DETERMINATIONS OF CAPILLARY SKIN RESISTANCE IN CHILDREN

Two methods have been advocated for the determination of the capillary skin resistance. First, there is the application of a positive pressure to the forearm for a certain period of time, being, in effect, a modified Rumpel-Leede test. Hess and Fish[6] applied this test to infants suffering with scurvy in 1914. Öhnell[7] in 1928 first suggested the use of this test in the recognition of latent scurvy, and Göthlin[8] (1931 and 1933) has reported extensive studies in an attempt to determine the least possible discernible deficiency of vitamin C. Ruth Stocking[9] in 1933 employed Göthlin's method in an effort to determine the frequency of mild cases of vitamin C deficiency in a relatively healthy group of children of preschool and early school age. Gedda[10] (1932) thought he could demonstrate a seasonal influence upon the capillary skin resistance by studying the same group of students in autumn and in spring. He found the number of petechiae in May was almost double the number in September in healthy subjects. Greene[11] in 1934 reported studies on a group of well-nourished preschool and school children as well as a group of malnourished school children with deficient vitamin C. His tests vary from those of Göthlin in that he tested both arms. Greene concludes that a positive reaction to the capillary resistance test does not necessarily denote deficient vitamin C in the diet.

The treatment of adult scurvy by means of ascorbic acid, when administered either orally or by intravenous injection, has been reported by Wright.[11a] A rapid improvement was noted as judged by the gen-

eral condition, disappearance of purpuric spots, cessation of bleeding, and a decrease in capillary fragility to within normal limits.

A second method for the determination of the capillary skin resistance is that originated by Hecht[12] (1907). By applying suction to the skin and thus creating negative pressure of varying degree for a certain length of time, the resistance of the skin capillaries may be tested. Dalldorf[13] in 1933, using his modification of da Silva-Mello's portable apparatus, employed the negative pressure method on a group of children of poor economic status. He believed that in a certain proportion of the children in this group who had been on a low vitamin C diet he was able to show capillary rupture at lower than normal pressures. He, therefore, concludes that by this test he was enabled to diagnose subclinical scurvy.

Brock and Malcus,[14] in a comprehensive review of the capillary skin resistance in more than 150 children, simultaneously compared the positive and negative pressure methods. In the latter method they further compared tests over the cubital fossae of both arms with tests over the subclavicular space on the chest. They believed that the positive pressure method is much less accurate than the negative pressure method. The results of the negative pressure test on the arms and chest showed some variations in the normal individual studies, the chest values tending to be somewhat lower. In pathologic conditions tests on both arms agreed well. Brock and Malcus were unable to obtain a case of scurvy on which to make determinations. In a case of thrombocytopenic purpura they obtained a low value for the capillary skin resistance. The decreased capillary skin resistance seemed to run parallel to the periods of hemorrhage in their case, although no relationship could be drawn to the increase and decrease in the number of platelets.

Lindquist[15] in 1935, using an apparatus similar to that described by Hecht, reported variations in capillary skin resistance when tested over different portions of the body. He also found a variation to occur with the age of the infant and child. In the discussion appended to Lindquist's report, Stoltenberg, using the positive pressure test, believed that he was able to show that capillary skin resistance was related to vitamin C content of the diet. Utheim-Toverud, in discussing Lindquist's paper, describes a case of scurvy in a nursing mother who had been on a low vitamin C diet during pregnancy and the nursing period. She was unable to demonstrate a lowered capillary skin resistance in this case of active scurvy by using the positive pressure method. Recently Dalldorf and Russell[16] reported that the parenteral injection of cevitamic acid in individuals with a low capillary skin resistance test will give a prompt and prolonged rise in the capillary skin resistance. The rise was noted after one or two hours and remained elevated for six to seven hours following the test.

RESULTS

A. *Values Obtained in Infants and Children on an Adequate Vitamin C Dietary.*—Our results include determinations of the reduced cevitamic acid content in milligrams per cent of plasma from the newborn period to puberty in fifty-nine infants and children. The reduced cevitamic acid content of single specimens of the urine was also determined in the same group. The urinary determinations are given in milligrams per cubic centimeter. Likewise, the capillary skin resistance of this group was tested and is given in millimeters of mercury below atmospheric pressure.

We wish first to present data for the reduced cevitamic acid content of blood plasma, obtained simultaneously from blood from the umbilical cord of the infant and from the venous blood of the mother immediately subsequent to delivery. These values are given in Table I.

TABLE I

REDUCED CEVITAMIC (ASCORBIC) ACID CONTENT OF INFANT'S CORD BLOOD COMPARED WITH MATERNAL VENOUS BLOOD

CASE	1	2	3	4	5
Ascorbic acid in maternal blood, mg. per cent	1.43	0.872	1.334	0.667	0.821
Ascorbic acid in cord blood, mg. per cent	1.40	0.872	1.334	0.667	0.821

The values from the cord blood of the infant and from the venous blood of the mother are nearly identical. From this data we may conclude that there is a complete diffusion of cevitamic acid through the placenta into the fetal blood. The cevitamic acid content of the tissues of the fetus and newborn infant is, therefore, directly dependent upon the supply obtained from the mother. As far as we know, the mother obtains her supply of cevitamic acid from the diet. Whether she or her fetus will have a high or low concentration will depend upon the vitamin C content of her dietary. Unfortunately we did not obtain a sufficient dietary history from the mothers whose blood we examined. However, the variation from 0.667 to 1.43 mg. per cent would force one to conclude that the mother with the low plasma value had been on a meager vitamin C-containing diet, while the mother with the high value had been on an adequate vitamin C-containing diet.

Table II presents data in chronologic order from infants during the first week of life to children of thirteen years. All of these infants and children were on an adequate vitamin C-containing diet, and we believe that the figures represent norms for the age groups covered. The values for the cevitamic acid content of the blood plasma were determined as soon as possible after the withdrawal of the blood from a vein and are for that portion of the cevitamic acid which occurs in a reduced state in the blood. A few values for total cevitamic acid

TABLE II

NORMAL VALUES OBTAINED ON PATIENTS IN PEDIATRICS CLINIC OF NORTHWESTERN MEDICAL SCHOOL

SUBJECT	AGE	REDUCED ASCORBIC ACID		CAPILLARY RESISTANCE OF SKIN	COMMENTS	R.B.C. IN MILLIONS	HGB.	
		BLOOD MG. %	URINE MG. C.C.	MG. OF HG			GM.	%
O	3 da.	1.13		500	No jaundice.			
T	3 da.	1.61		600	No jaundice.			
K	4 da	0.90		600	No jaundice.			
D	5 da.	1.08		500	No jaundice.			
C	6 da.	0.752		500	Very slight jaundice.			
E	6 da.	1.24		600	No jaundice.			
N. K. (c)	7 wk.	1.180		300	Breast plus O.J.* daily.	4.520	13.4	92
W. E.	2 mo.	0.975	0.001448	500	Formula plus O.J. daily.			
D. V.	2 mo.	1.29	0.02571	400	Breast plus O.J. daily.	3.650	11.8	80
F. P.	2 mo.	1.237	0.003140	350	Breast plus O.J. daily.	3.365	10.6	73
C. M.	2½ mo.	1.232	0.002416	450	Whole milk formula. Very small amount O.J. daily.			
C. B.	3 mo.	2.416	0.2519	400	Breast plus O.J. daily.	3.570	10.0	70
D. H.	3 mo.	1.007	0.001611	250	Formula plus O.J. daily.	3.430	10.0	70
H. L.	4 mo.	1.01	0.001286		Breast plus O.J. daily.	3.990	9.6	68
L. W. (c)	5 mo.	1.166		550	Breast plus O.J. daily.	5.710	11.8	80
J. S.	6 mo.	1.85	0.008036	350	Breast plus O.J. daily.	4.570	11.3	77
D. E.	6½ mo.	1.234	0.0026	450	Formula plus O.J. daily.	4.645	12.4	84
J. G.	7 mo.	1.155	0.003283	450	Breast plus O.J. daily.	4.920	12.2	84
J. W. (c)	8 mo.	0.832	0.002155	300	Formula plus O.J. daily.	4.250	9.2	62
R. J.	9½ mo.	0.968	0.002844	550	Breast plus O.J. daily.	4.380	10.8	74
F. J. (c)	11 mo.	1.568	0.0680	250	Breast plus O.J. daily.	4.840	11.2	76
D. M.	1 yr.	1.168	0.00499	550	Cow's milk, vegetables, O.J. daily.	5.150	8.4	58
D. F.	16 mo.	1.129	0.006197					
C. W. (c)	17 mo.	1.771	0.001664		Whole milk, 4 oranges daily.			
D. K.	19 mo.	0.909	0.01246	250	Vegetables, fruit, oranges daily.	5.250	9.8	69
A. K.	2 yr.	1.236	0.003283	250	Qt. milk, O.J. daily.	5.300	10.2	70
L. D.	2 yr.	1.560	0.003423	350	O.J. daily. Cooked vegetables and fruits.	4.630	11.2	76
W. H.	2 yr.	2.232	0.003895	300	O.J. every other day.			

*O.J. = orange juice.
(c) = negro patients

TABLE II—CONT'D

SUBJECT	AGE	REDUCED ASCORBIC ACID		CAPILLARY RESISTANCE OF SKIN	COMMENTS	R.B.C. IN MILLIONS	HGB.	
		BLOOD MG. %	URINE MG. C.C.	MG. OF HG			GM.	%
J. G. (c)	2 yr.	1.298	0.00899	250	Few fruits or vegetables.	4.635	12.0	82
G. S.	2½ yr.	1.61	0.001410	450	O.J. daily. Raw vegetables.	4.070	11.8	80
M. S.	2½ yr.	0.890	0.00299	300	O.J. daily. Raw fruit and vegetables.			
T. J.	2¾ yr.	1.644	0.0235	100	Oranges and apples daily.	4.800	11.4	78
M. O.	3 yr.	0.819	0.00782	450		4.710	12.4	83
J. D.	3 yr.	1.344	0.001804	200	O.J. daily, much milk, cooked vegetables.	4.350	12.6	88
E. L.	3 yr.	1.101	0.001578	450		4.900	11.8	80
R. B.	3½ yr.	2.033	0.01723	400	High carbohydrate diet.	4.670	11.6	78
B. K.	4 yr.	1.812	0.004027	250	Eats all fruits and vegetables.	4.260	11.6	78
T. B.	4 yr.	0.802	0.002311	500	High carbohydrate diet.	4.980	10.2	70
M. J.	5 yr.	1.220	0.0112	350	O.J. daily.	4.770	13.0	89
D. B. (c)	5 yr.	0.887	0.00404	450	Cooked vegetables.	4.790	12.0	82
R. B.	5 yr.	0.821	0.0009019	250	Oranges daily.	5.140	12.8	88
W. M.	6 yr.	0.859	0.001301	300	Three to four oranges per week. Apples frequently.	4.720	12.8	88
E. D.	6 yr.	1.637	0.009967	350	Apples frequently.	5.590	10.6	73
C. P.	6 yr.	2.025	0.01026	300	O.J. daily, many raw vegetables.	5.140	12.2	84
M. W. (c)	7 yr.	0.802	0.01108		"Green" vegetables.			
H. H.	7 yr.	1.56	0.0104	400		4.450	12.2	83
W. E. (c)	7 yr.	1.388	0.007806	200	Restricted diet for past 2 weeks because of discontinuance of "relief."	6.280	14.2	98
J. J. (c)	7 yr.	0.914	0.12636	200	Asthmatic. Until 4 yr. could take no citrous fruits; can take them now.	5.660	12.8	88
K. P.	9 yr.	1.374	0.04504	425	Fruits and vegetable daily.			
V. Z.	11 yr.	0.827	0.00222	400		4.150	10.8	74
H. C.	11 yr.	0.872	0.001642	300	Fruit occasionally.	5.290	10.8	74
C. W. (c)	11 yr.	0.879		200	Apples daily, oranges frequently.			
P. H.	13 yr.	1.031	0.00383	400	Oranges frequently.			
B. M.	13½ yr.	0.819	0.00835	300	No fruit since return from Ridge Farm week ago.	5.570	11.0	73

determined by treatment with hydrogen sulphide were made, but these have not been included. The values for the blood plasma range from a low of 0.752 mg. per cent in a six-day-old infant to a high of 2.416 mg. per cent in a three-month-old breast-fed infant who was receiving orange juice daily. We have not averaged the values obtained for individuals of similar ages, but it is our impression that there is a direct relationship between the values for the reduced cevitamic acid in the blood and the vitamin C intake in the diet. The urinary values determined according to the method of Harris and Ray[17] are on single voided specimens and are not as informative as the blood values. The values for capillary skin resistance were uniformly high in the infants under one week of age. The skin of these newborn babies was ruddy and petechiae or diffuse reddening of the skin was not noted under 500 mm. of negative pressure. Aside from this age group we were unable to observe correlation between age and the cevitamic acid content of the blood plasma. Red blood cell counts and hemoglobin values show no relationship to either cevitamic acid content of the blood and urine or to capillary skin resistance.

In Table III we have noted the relationship of the capillary skin resistance at negative pressures varying from 100 to 500 mm. of mercury, or over, to the reduced cevitamic acid in the blood plasma of the individuals listed in Table II. We are unable to demonstrate a definite relationship.

TABLE III

CAPILLARY RESISTANCE OF SKIN AND ASCORBIC ACID IN BLOOD PLASMA

CAPILLARY RESISTANCE OF SKIN MM. OF HG	100	200	250	300	350	400	425	450	500 OR OVER
Ascorbic acid in blood plasma. mg. per cent	1.644	1.388	1.812	2.232	1.850	2.146	1.374	1.234	1.168
		1.344	1.568	2.025	1.637	2.003		1.232	1.166
		0.914	1.298	1.180	1.560	1.560		1.155	0.975
		0.879	1.236	0.890	1.237	1.290		1.110	0.968
			1.007	0.872	1.220	1.031		1.101	0.802
			0.909	0.859		0.827		0.887	
			0.821	0.832				0.819	
				0.819					

B. *Values Obtained in Infants and Children on a Low Vitamin C Dietary.*—In Table IV we present a group of apparently normal children ranging in age from six weeks to eleven years who had been on diets low in cevitamic acid. The blood plasma values in this group range from 0.513 mg. per cent to 0.769 mg. per cent. The urinary values in single specimens are low, and the tests of the capillary skin resistance vary from 150 to 500 mm. of mercury negative pressure. We can conclude that with the low dietary intake the values for blood and urine are consistently lower than in Table II in which the

TABLE IV

SUBNORMAL VALUES OBTAINED ON PATIENTS IN PEDIATRICS CLINIC OF NORTHWESTERN MEDICAL SCHOOL

SUBJECT	AGE	ASCORBIC ACID SINGLE SPEC.		CAPILLARY RESISTANCE OF SKIN	COMMENTS	R.B.C. IN MILLIONS	HGB.	
		BLOOD MG. %	URINE MG./C.C.	MM. OF HG			GM.	%
M. T.	6 wk.	0.752	0.001983	450	Very little orange juice.	4.250	10.5	72
C. A.	2 mo.	0.702		500	Very little orange juice.	3.800	10.6	76
C. U.	5 mo.	0.739		500	Juice ½ orange daily.			
M. T.	6 mo.	0.675		400	Very little orange juice.	4.510	11.6	79
W. P.	8 mo.	0.513		400	Orange juice discontinued because of rash.	4.920	11.6	79
K. L.	17 mo.	0.698	0.006309	200	Very little orange juice.	4.760	10.4	72
D. W.	20 mo.	0.528			Very little orange juice.			
P. W.	3 yr.	0.769	0.00190	400	No orange juice. Whole milk.	4.440	12.4	84
D. E.	4 yr.	0.697	0.00154	400	Orange juice daily. Cooked vegetables	4.645	12.4	84
G. B.	5 yr.	0.760	0.001664	500	High carbohydrate diet.	4.130	10.2	74
G. B.	5 yr.	0.688	0.00282	250	Oranges occasionally.	5.160	12.0	80
L. H.	10 yr.	0.718	0.001804	150	Bread and butter main diet.	5.510	14.2	98
G. H.	11 yr.	0.688	0.00171					
C. B.	11 yr.	0.572	0.00111	300	Oranges occasionally.	4.870	11.2	77

TABLE V

EFFECT ON YOUNG ADULTS OF FEEDING ONE PINT OF ORANGE JUICE DAILY FOR ONE WEEK

NAME AND AGE IN YR.	DATE	REDUCED ASCORBIC ACID CONTENT			COMMENTS
		URINE SINGLE SPEC. MG./C.C.	SALIVA MG. %	BLOOD MG. %	
B. I. 32	2/ 8/35	0.00685	0.275	1.375	Oranges daily until 2 days before test.
	2/12/35 A.M.	0.0827	0.137		
	P.M.	0.01140	0.106		
	2/13/35		0.212		
	2/15/35	0.1150	0.300	1.463	
R. M. 22	2/ 8/35	0.00151	0.307	1.030	Citrous fruit once a day.
	2/12/35	0.00143	0.152		
	2/13/35 A.M.	0.00401	0.106		
	P.M.	0.00188	0.106		
	2/15/35	0.00222	0.180	1.35	
D. M. 22	2/ 8/35	0.00735	0.183	1.603	Citrous fruit daily.
	2/12/35 A.M.	0.00616	0.106		
	P.M.	0.00590	0.122		
	2/13/35	0.01260	0.106		
	2/15/35	0.10800	0.180	1.35	
A. M. 21	2/ 8/35	0.00413	0.336	0.687	Citrous fruit occasionally.
	2/12/35	0.00502	0.0912		
	2/13/35 A.M.	0.00426	0.1060		
	P.M.	0.00239	0.167		
	2/15/35	0.00495	0.150	1.35	
R. R. 22	2/ 8/35	0.00473	0.275	2.29	At least 2 oranges daily.
	2/12/35 A.M.	0.00483	0.0912		
	P.M.	0.00903	0.106		
	2/13/35	0.00639	0.106		
	2/15/35	0.12000	0.180	2.36	
J. S. 21	2/ 8/35	0.00272	0.244	0.916	Citrous fruit occasionally.
	2/12/35 A.M.	0.00752	0.152		
	P.M.	0.00852	0.152		
	2/13/35	0.00996	0.0912		
	2/15/35	0.01340	0.180	1.35	
R. S. 21	2/ 8/35	0.00242	0.244	0.802	Rarely eats fruit but eats all vegetables and likes slaw especially.
	2/12/35 A.M.	0.00200	0.0912		
	P.M.	0.00213	0.137		
	2/13/35	0.00213	0.106		
	2/15/35	0.00242	0.210	1.463	
F. S. 21	2/ 8/35	0.00109	0.183	0.916	Occasional orange.
	2/12/35 A.M.	0.00276	0.0912		
	P.M.	0.00138	0.122		
	2/13/35	0.00251	0.0912		
	2/15/35	0.00444	0.090	1.463	
E. P. W. 22	2/ 8/35	0.00328	0.183	1.488	Citrous fruit daily.
	2/12/35	0.00765	0.137		
	2/13/35 A.M.	0.00980	0.106		
	P.M.	0.01030	0.122		
	2/15/35	0.01060	0.180	1.575	
L. W. 22	2/ 8/35	0.00352	0.275	0.802	Citrous fruit daily.
	2/12/35	0.00351	0.106		
	2/13/35 A.M.	0.00338	0.137		
	P.M.	0.00188	0.0912		
	2/15/35	0.00420	0.150	1.35	
E. S. W. 22	2/ 8/35	0.00160	0.275	1.145	Citrous fruit daily.
	2/12/35 A.M.	0.00251	0.106		
	P.M.	0.00431	0.106		
	2/13/35	0.00488	0.0912		
	2/15/35	0.02270	0.180	1.35	

diets were fortified with adequate amounts of vitamin C-containing foods. The lowest capillary skin resistance was 150 mm. of mercury with a corresponding blood value of 0.718 mg. per cent. The lowest blood value was 0.513 mg. per cent for which a capillary skin resistance of 400 mm. of mercury was noted. These results point to no definite correlation between the two tests.

C. *Values Obtained for Young Adults After One Week on a High Vitamin C Dietary.*—Table V gives the results for the feeding of one pint of orange juice daily for one week to a group of young adult medical students ranging in age from twenty-one to thirty-two years. These results are for the reduced cevitamic acid content of the blood plasma and saliva in milligrams per cent and single specimens of urine in milligrams per cubic centimeter. The saliva determinations were made according to the method described by Stuteville[18] working in these laboratories. The first determinations were made at the beginning of the week before the dietary of one pint added orange juice per day was commenced. Those individuals who had previously had a low vitamin C intake showed low initial blood plasma values. Thus student A. M. who ate citrous fruits only occasionally showed an initial value of 0.687 mg. per cent. After taking one pint of orange juice in addition to his regular diet for one week, it will be noted that his blood value had risen to 1.35 mg. per cent. The same rise was observed in other students on a low initial vitamin C diet; J. S., 0.916 to 1.35 mg. per cent; R. S., 0.802 to 1.463 mg. per cent; F. S., 0.916 to 1.463 mg. per cent; L. W., 0.802 to 1.35 mg. per cent. The increase in urinary values was most pronounced in those individuals who had the higher blood values to begin with and who had been on a generous C dietary prior to the experiment. This is clearly shown in the cases of B. I., D. M., R. R., E. P. W., and E. S. W. The significance of the urinary rise will be discussed later.

The salivary findings are included solely for the purpose of demonstrating this channel of excretion. Experiments have been planned which will make a more quantitative comparison of the salivary and blood cevitamic acid levels possible.

D. *Values Obtained After Oral Administration of Cebione to a Group of Individuals Who Had Previously Been on a Low Vitamin C. Dietary.*—This is a small, miscellaneous group of individuals who for one reason or another had been on a dietary low in vitamin C content for a considerable time (Table VI). The first infant, E. R., one-year-old male, had received no orange juice since birth. His parents were of poor economic status and were at first inclined to be uncooperative. The infant showed no definite signs of scurvy though he was underweight, poorly nourished, and irritable. The blood plasma value obtained on his first visit to the clinic was 0.67 mg. per cent. Nineteen

days later he was brought to the clinic by his mother who stated that she had given him one ounce or more of orange juice daily as advised. The blood plasma value obtained on this visit was 0.513 mg. per cent. An experienced social worker was called in consultation, and the mother admitted that the infant had had no orange juice in the nineteen-day interval between visits. With the aid of the social service worker the mother was then convinced that if she persisted in omitting vitamin C from the diet, the child would no doubt soon show signs of scurvy. The mother was given a supply of 10 mg. cebione tablets (Merck and Co., Inc.) and was instructed to dissolve one tablet in one-half ounce of water, which was to be administered three times daily before meals. The mother carried out these instructions and returned to the clinic one week later. At this visit the cevitamic acid content of the blood plasma was 1.681 mg. per cent, which is a considerable increase over the previous value. The infant showed none of the irritability of the two former visits. The mother was then instructed to include one ounce or more of orange juice in the daily dietary of the infant, and two months later the child was in a greatly improved nutritional state, with a blood plasma cevitamic acid value of 1.050 mg. per cent.

TABLE VI

PATIENTS WITH SUBNORMAL BLOOD VALUES TREATED WITH CEBIONE

SUBJECT AND AGE	ASCORBIC ACID CONTENT			SALIVA MG. %	CAPILLARY RESISTANCE OF SKIN MM. OF HG	COMMENTS
	BLOOD MG. %	URINE MG./C.C.	URINE, 24 HR. SPECIMEN			
E. R. 1 yr.	0.671					No orange juice since birth.
	0.513					19 days later still no orange juice.
	1.681					30 mg. cebione daily for one week.
	1.050					2 mo. later, had been having orange juice daily.
M. H. 9 yr.	0.675		3.42	0.187	300	No fruits or vegetables for some time.
	1.773		5.982	0.195	350	50 mg. cebione daily for two weeks.
E. H. 11 yr.	0.675		2.52	0.187	300	No fruits or vegetables for some time.
	1.333		13.007	0.280	400	50 mg. cebione daily for two weeks.
D. W. Adult	0.675	0.00606		0.240	450	Seldom eats any citrous fruits. Sensitive to them.
	2.01	0.0239		0.258	350	60 mg. cebione daily for one week.
E. G. Adult	0.34					Severe anemia. Had been living on diet of oatmeal for a year.
	1.039					Hospital diet for 3 wk. 30 mg. cebione daily.
	0.697					Cebione discontinued for 10 days.

Two brothers, M. H., aged nine years, and E. H., aged eleven years, had refused to eat fruits or vegetables for several months. A visit to the dentist revealed a number of cavities in the teeth of the older child. The dentist, upon questioning the mother, discovered the dietary vitamin C deficiency. The initial blood serum values for each child were 0.675 mg. per cent. Five 10 mg. cebione tablets (50 mg.) daily were prescribed orally for fourteen days. At the end of this period a considerable rise in the blood plasma cevitamic acid of each child was noted. The urinary output in twenty-four-hour specimens had also increased over the initial values. There was a slight increase in the capillary skin resistance of each of the brothers following the fourteen-day period of the administration of cebione.

D. W., an adult, said that he seldom ate any citrous fruits because he felt that their ingestion caused him various allergic manifestations. His initial blood plasma value was 0.675 mg. per cent, and after oral administration of six 10 mg. cebione tablets (60 mg.) daily the blood plasma value rose to 2.01 mg. per cent. The cevitamic acid value in the single specimen of urine was also greatly increased. The capillary skin resistance showed a decrease from 450 to 350 mm. of mercury.

E. G., an adult, was admitted to the hospital with a severe anemia. He had been living on a diet which consisted mainly of oatmeal for nearly three years. He had been on a mixed hospital diet for three weeks. The initial blood plasma value was 0.34 mg. per cent. Three 10 mg. cebione tablets (30 mg.) were administered daily for nineteen days. The ascorbic acid content of the blood plasma was then 1.039 mg. per cent. The cebione tablets were discontinued for ten days, and the value dropped to 0.697 mg. per cent.

DISCUSSION

The values for the reduced cevitamic acid content of the blood plasma here presented, we believe, parallel the intake of vitamin C in the dietary of the individual. It may be concluded from these data that blood plasma values less than 0.75 to 0.80 mg. per cent of reduced cevitamic acid indicate a subnormal vitamin C intake. The method presented, while it does not measure the total cevitamic acid of the blood plasma, is of clinical value because it is accurate and reliable and of easy technical performance, and the results may be quickly obtained. We believe that blood plasma values obtained by the method described will prove to be an accurate means for the detection of subclinical scurvy (latent scurvy or hypovitaminosis C) caused by an inadequate vitamin C intake in the diet. The accuracy and usefulness of the test were forcefully impressed upon us by the incident described under case E. R. in Table VI. When the second blood test on this infant, taken after a nineteen-day interval, over which period the mother maintained she had given considerable daily

amounts of orange juice, was lower than that taken at the first examination, we obtained a confession from the mother that no orange juice had been given. Following the daily oral administration of 30 mg. of cebione for one week, the blood plasma value was nearly trebled.

Our results for ambulatory infants and children on adequate vitamin C-containing diets have given us a standard for the reduced cevitamic acid content of the blood plasma, and from these norms we have been able to substantiate and prove in individual cases a low vitamin C intake in the diet. As far as we know, this is the first series of data to be published showing cevitamic acid blood plasma values for infants and children on adequate vitamin C-containing diets. It is also the first report to demonstrate the efficacy of blood plasma values in determining subclinical scurvy.

From the close agreement of the values which were obtained on the cord blood of the infant and the venous blood of the mother immediately following delivery, we have concluded that the infant in utero has received his supply of vitamin C through the placental circulation. The variation in the values which were obtained on the different mothers led us to assume that the maternal dietary for a variable period preceding delivery determined the content of cevitamic acid in the blood plasma of the newborn infant. After the newborn period, the blood plasma values for reduced cevitamic acid have apparently followed the dietary intake of vitamin C in the various age periods from infancy through childhood.

Of other tests employed in the attempt to determine normal vitamin C intake in the dietary and deficient intake resulting in subclinical scurvy, the positive pressure and negative pressure suction methods for determining capillary skin resistance have already been noted.

We have employed the newly devised apparatus of Cutter and Johnson[3] and have attempted to correlate the values for capillary skin resistance thus obtained with blood plasma values for reduced cevitamic acid and the dietary histories. As pointed out in Tables III and IV, we have been unable to correlate either adequate or insufficient vitamin C dietary with capillary skin resistance, as determined by this refined and easily operated apparatus for producing suction by negative pressure over the skin. Even in cases with an initial low blood plasma value, the initial capillary skin resistance was not correspondingly decreased. In Table VI, M. H. showed a rise of 50 mm. and E. H. a rise of 100 mm. of pressure following oral administration of cebione, while their blood plasma values showed a relatively greater increase. However, D. W., with a marked rise in blood plasma value, showed a decrease of 100 mm. in his capillary skin resistance following ingestion of cebione.

There is a considerable variance of opinion in the literature as to the relationship of the capillary resistance of the skin to vitamin C nutrition. We conclude from our results that the blood plasma values for cevitamic acid have given us a far more sensitive method for determining adequate or insufficient vitamin C dietary than have the values for capillary skin resistance.

We were able to examine only single specimens of urine from the group of ambulatory infants and children upon whom we have reported. Likewise in the group of young adults studied, we were able to examine only daily single specimens. From two of the patients on low vitamin C diets treated with cebione, we were able to collect twenty-four-hour specimens. The examination of single urine specimens for cevitamic acid content does not give as much information as a single blood examination, and the same is true of examination of a single twenty-four-hour specimen. It will be noted from Table II that there is a considerable variation of high and low urinary values for infants and children on adequate vitamin C dietary. If we compare these values with those of Table IV for infants and children on a low vitamin C dietary, it will be noted that the urinary values run consistently lower than those for patients in Table II. The urinary values in Table V will aid us in the explanation of the value of such determinations. The initial blood plasma value for student B. I. (Table V) was high, 1.375 mg. per cent, and increased somewhat to 1.463 mg. per cent. The initial urinary value was low but increased daily, so that after taking one pint of orange juice each day for one week the value in the single specimen on the final day was approximately twenty times greater. (The value at the beginning of the experiment was 0.00685 mg. per cubic centimeter; at the end, 0.1150 mg. per cubic centimeter.) This individual had been on an adequate vitamin C diet until two days previous to the experiment. We may suppose from her blood plasma value that her tissues were near the saturation point for cevitamic acid. The large amounts of orange juice taken daily for the week of the experiment saturated her tissues, and the excess amount of cevitamic acid was excreted in the urine as shown by the high value on the last day.

In contrast to this experiment, student A. M. of Table V rarely included citrous fruits in his diet and was on a low vitamin C intake prior to the experiment. His preliminary blood plasma value was low, 0.687 mg. per cent. Following one week of the daily intake of one pint of orange juice, his blood plasma had risen to 1.35 mg. per cent. This value approximately equals the initial value for student B. I. (B. I.'s initial value, 1.375 mg. per cent; A. M.'s final value, 1.35 mg. per cent.) The urinary values for A. M. remained nearly constant throughout the experiment. (Initial value 0.00413 mg. per cubic centimeter; final value 0.00495 mg. per cubic centimeter.) These

results clearly indicate that the tissues of student B. I., on adequate vitamin C intake prior to the experiment, reached their saturation point, and the excess cevitamic acid was excreted as an overflow in the urine causing the final urinary value to be high. On the other hand, the tissues of student A. M., who had been on a low vitamin C diet previous to the experiment, had not yet become saturated at the end of the experiment and were still taking up the cevitamic acid of the diet. However, the tissue level must have been considerably increased at the end of the experiment judging from the higher blood plasma value. As saturation had not been reached in this instance there was no overflow, and the final urinary value was approximately the same as the initial value.

The twenty-four-hour urine results on brothers M. H. and E. H., in Table VI, are also an excellent example of tissue saturation with cevitamic acid and urinary overflow. Each of the brothers had been on a previously low vitamin C intake. This fact is substantiated by their initial low blood plasma values. Following the ingestion of 50 mg. of cebione daily for fourteen days, their blood plasma values showed marked increase. The twenty-four-hour urinary values, particularly in the case of E. H., were also greatly increased. From these results we may conclude that the high vitamin C intake had caused the tissues of these two patients to become saturated and an overflow excretion into the urine was noted by the high values for cevitamic acid in the final twenty-four-hour urine specimens. We may conclude from these results that, while single blood plasma values will show accurately the relative state of the body in regard to whether vitamin C nutrition has been previously high or low, it is necessary to follow a series of single or preferably twenty-four-hour urine specimens to determine tissue saturation. Individual single or twenty-four-hour urine specimens will give us only a little information as to the previous vitamin C dietary of the individual, or as to the degree of tissue saturation.

Among the first reports to describe the estimation of cervitamic acid in the urine were those of Harris, Ray, and Ward[19] and of van Eekelen, Emmerie, Josephy, and Wolff.[20] Alfred F. Hess and Helen Rivkin Benjamin[21] were among the first to study urinary excretion in the infant, and they believed that under ordinary nutritional conditions vitamin C is not excreted in appreciable amounts in human urine. They thought that the ingestion of excessively large amounts of vitamin C leads to urinary excretion after the body stores have become completely saturated.

Harris and Ray,[17] in studying infants suffering from active scurvy or those with a history of a previous low vitamin C diet, have very clearly shown that the urinary excretion of cevitamic acid is less than that of normal infants. They have further shown that if a large single

dose of vitamin C be given to a normal infant, there will be a marked increase in the urinary excretion. For the infant with scurvy or low previous vitamin C intake, the single dose of cevitamic acid causes very slight, if any, increase in the urinary excretion. After this latter group of infants has been fed on a diet rich in cevitamic acid for a certain period, and the tissues saturated, a single large dose of cevitamic acid will cause an increased urinary excretion similar to that obtained in the normal infant. The values given by Harris and Ray were about ten times greater than those reported by Hess and Benjamin for apparently normal infants.

Von Drigalski[22] has investigated the excretion of cevitamic acid in the urine of children. His values were approximately 50 per cent higher than those given by Harris and Ray, and he concludes that the low values reported by Hess and Benjamin may have been due to errors in technic.

Rohmer, Sanders, and Bezssonoff[23] have stated that they believed that infants under five months of age were able to synthesize vitamin C in the body. The only evidence which they offered for this conclusion was the fact that the babies examined by them continued to excrete cevitamic acid in the urine for forty-eight hours after they had been on a "scorbutic" diet. From our own data and the literature here quoted, it can be seen that the reserve cevitamic acid stored in the tissues could much better account for the excretion noted over the forty-eight-hour period when no vitamin C was given. In Table IV it will be noted that five infants ranging from six weeks to eight months of age, all of whom had been on a very low vitamin C intake, showed correspondingly low blood plasma values. Had these infants the ability to synthesize cevitamic acid, we would expect to find blood plasma values equal to those for children on an adequate vitamin C-containing diet.

It should be mentioned that cevitamic acid is unstable in the urine and specimens should either be titrated immediately when passed, or they should be collected in a container with sufficient glacial acetic acid to be approximately 10 per cent concentration after the addition of the urine. By the addition of glacial acetic acid, we have found that test specimens, if kept under refrigeration for as long as from twelve to twenty-four hours, will closely check the values obtained when freshly passed.

CONCLUSIONS

1. A method has been described for determining the reduced ascorbic acid content of the blood plasma. Such a determination accurately indicates the nutritional state of the body relative to vitamin C.

2. In a group of infants and children from the newborn period through the thirteenth year, who had been on a previously adequate

vitamin C dietary, we have presented a normal range of values for the reduced cevitamic acid content of the blood plasma.

3. Using the instrument devised by Cutter and Johnson for determining the capillary skin resistance by suction in millimeters of negative pressure, we present values in this group of infants and children on adequate vitamin C dietaries.

4. A comparison of the cevitamic acid blood plasma values with the values obtained for capillary skin resistance in this group on a previously adequate vitamin C dietary showed no uniform or constant agreement.

5. Similar results are presented for an apparently normal group of infants and children on a previously low vitamin C dietary. The blood plasma values for cevitamic acid in this group are all correspondingly low, and the capillary skin resistances are not consistently lower in this group.

6. The results for the determination of the reduced cevitamic acid content of the blood plasma obtained simultaneously from the cord blood of the infant and the venous blood of the mother immediately subsequent to delivery are presented. These values are nearly identical, and it may be concluded that there is a complete diffusion of cevitamic acid through the placenta and into the fetal blood.

7. Although there is an almost identical agreement between the value for the reduced cevitamic acid content of the blood plasma of the mother and her infant, there is a marked variation for these values in the different mothers. We have assumed from this variation that the value for the reduced cevitamic acid in the blood plasma of the newborn infant is dependent upon the diet of the mother in regard to vitamin C for a period previous to the delivery of the infant.

8. Daily determinations of the reduced cevitamic acid content of the blood plasma, saliva, and single urine specimens for a group of young adults fed one pint of orange juice daily for one week are presented and discussed. From this experiment we have been able to demonstrate the saturation of the tissues with cevitamic acid and an overflow into the urine and excretion beyond the saturation point.

9. In a small group of individuals who had been on a low previous vitamin C dietary for a considerable time, we were able to demonstrate the effectiveness of the oral administration of cevitamic acid.

10. We believe that values obtained for the reduced cevitamic acid content of the blood plasma here described will prove to be a convenient, rapid, and accurate method for the detection of subclinical scurvy (latent scurvy or hypovitaminosis C).

We wish to acknowledge our indebtedness to Miss Elizabeth Smith for her technical assistance and to Miss Florence Olmstead of the Pediatrics Clinic for her assistance in the clinical part of this study.

REFERENCES

1. Abt, A. F., and Epstein, I. M.: J. A. M. A. **104**: 634, 1935.
2. Farmer, C. J., and Abt, A. F.: Proc. Soc. Exper. Biol. & Med. **32**: 1625, 1935.
3. Cutter, I. S., and Johnson, C. A.: J. A. M. A. **105**: 505, 1935.
4. Gabbe, E.: Klin. Wchnschr. **13**: 1389, 1934.
5. Mirsky, I. A., Swadesh, S., and Soskin, S.: Proc. Soc. Exper. Biol. & Med. **32**: 1130, 1935.
6. Hess, A. F., and Fish, M.: Am. J. Dis. Child. **8**: 386, 1914.
7. öhnell, H.: Acta med. Scandinav. **68**: 176, 1928.
8. Göthlin, G. F.: Skandinav. Arch. f. Physiol. **61**: 255, 1931.
   Göthlin, G. F.: J. Lab. & Clin. Med. **18**: 484, 1933.
9. Stocking, R. E.: Arch. Pediat. **50**: 823, 1933.
10. Gedda, K. O.: Skandinav. Arch. f. Physiol. **63**: 306, 1932.
11. Greene, D.: J. A. M. A. **103**: 4, 1934.

11a. Wright, I. S.: Proc. Soc. Exper. Biol. & Med. **32**: 475, 1934.

12. Hecht, A. F.: Jahrb. f. Kinderh. **65**: 113, 1907.
13. Dalldorf, G.: Am. J. Dis. Child. **46**: 794, 1933.
14. Brock, J., and Malcus, A.: Ztschr. f. Kinderh. **56**: 237, 1934.
15. Lindquist, N.: Acta. paediat. (supp. 1) **17**: 247, 1935.
16. Dalldorf, G., and Russell, H.: J. A. M. A. **104**: 1701, 1935.
17. Harris, L. J., and Ray, S. N.: Lancet **1**: 71, 1935.
18. Stuteville, O. H.: Proc. Soc. Exper. Biol. & Med. **32**: 1454, 1935.
19. Harris, L. J., Ray, S. N., and Ward, A.: Biochem. J. **27**: 2011, 1933.
20. Van Eekelen, M., Emmerie, A., Josephy, B., and Wolff, L. K.: Klin. Wchnschr. **13**: 564, 1934.
21. Hess, A. F., and Benjamin, H. R.: Proc. Soc. Exper. Biol. & Med. **31**: 855, 1934.
22. Von Drigalski, W.: Ztschr. f. Vitaminforsch. **4**: 128, 1935.
23. Rohmer, P., Sanders, U., and Bezssonoff, N.: Synthesis of Vitamin C by the Infant. Nature, London **134**: 142, 1934.

303 East Chicago Avenue

INDIGO CARMINE FOR THE QUANTITATIVE DETERMINATION OF GLUCOSE IN CEREBROSPINAL FLUID

DAVID J. COHN, PH.D., AND ABRAHAM LEVINSON, M.D.
CHICAGO, ILL.

A KNOWLEDGE of the glucose content of cerebrospinal fluid is a valuable aid in the differentiation of meningitis from other diseases.[1] The glucose content of the cerebrospinal fluid obtained by lumbar puncture from nonmeningitic patients ranges from about 35 to 75 mg. per 100 c.c.,[2] whereas in untreated meningitis glucose is often absent from the lumbar fluid or present in amounts very much below the normal range.

To determine the presence or absence of glucose, qualitative methods depending on Fehling's or similar reagents are often used, but they do not give sufficiently exact results to be of much diagnostic value. The quantitative methods which have been employed for glucose determination in cerebrospinal fluid are rather complicated, being either the same as those for glucose determination in blood or modifications of these methods. The copper reagents used in most blood sugar methods are sensitive to proteins and other substances present in the cerebrospinal fluid, as well as to glucose, and it is therefore necessary to precipitate the proteins and either to centrifuge or filter them off. Subsequent treatment is then required so that the amount of the reduced copper may be determined either by iodometric titration or by measurement with a colorimeter of the amount of colored substances formed.

The need has been felt for a less involved procedure, and such a method, designed primarily for use with cerebrospinal fluid, is here described. It requires a minimum of time and apparatus and is, therefore, especially suited to the needs of the clinicans, who often desire to know the glucose content of the cerebrospinal fluid at times and places at which full laboratory facilities are not available. This method is based on color changes from blue through violet, purple, red, and orange to yellow, which the dye, indigo carmine, undergoes when heated with glucose in alkaline solution. The color formed depends on the proportion of the dye which is reduced to the leuco form. If sufficient glucose is present, the complete change to yellow takes place; with smaller amounts of sugar the reaction stops at one

From the Department of Biochemistry of the Nelson Morris Memorial Institute and from the Sarah Morris Hospital for Children, Michael Reese Hospital.

of the intermediate colors. In cerebrospinal fluid—even when it is heavily purulent—no substances, aside from glucose, are present which appreciably affect the dye. It is therefore merely necessary to heat together measured amounts of the cerebrospinal fluid and the reagent and note the color produced. Since the tint, rather than the depth of color, is the measure of the amount of glucose present, comparison can be made with a color chart, and no instrument is necessary.

Dyestuffs, especially methylene blue, have been proposed previously for glucose determination.[3] The difficulty with such methods has usually been that considerable error is brought about by reoxidation of the dye by the oxygen of the air during, or immediately following the reaction. This difficulty is overcome in the present method by the use of a paraffin plug, which keeps the solution out of contact with the air. Indigo carmine has been used under the name of "Mulder's reagent" for detecting the presence of glucose in urine, but no quantitative application has heretofore been made.

APPARATUS AND REAGENTS

The reaction is carried out in a small test tube, 100 × 10 mm., calibrated at 2, 4, and 5 c.c. The cerebrospinal fluid and the reagents are transferred to the tube with an "eye dropper" pipette. As an alternative, an uncalibrated tube may be used, and the solutions measured with calibrated pipettes.

A small pot or beaker is provided for use as a water-bath.

The reagents required are:

1. Indigo carmine, 0.1 gm. per 100 c.c.
2. Sodium carbonate, anhydrous 2.1 gm. per 100 c.c.
3. Paraffin plugs prepared in the form of little cylinders that slip easily into the test tubes. (These are cut out of blocks of paraffin with a cork borer.)

PROCEDURE

Measure 2 c.c. each, of the indigo carmine and sodium carbonate solutions into a test tube.

Add 1 c.c. of cerebrospinal fluid, mix, and drop in a paraffin plug.

Place in a beaker and keep at the boiling point for five minutes.

Cool until the paraffin hardens and compare with the color chart.

Since the amount of pure dye varies in the commercial preparations obtainable, it is necessary to standardize the solutions. This standardization, as well as the preparation of a chart for color comparisons, may be carried out simultaneously by running a series of determinations with glucose solutions of known concentration in place of cere-

brospinal fluid. The test glucose solutions should give the following colors when heated with alkaline indigo carmine:

MG. GLUCOSE PER 100 C.C.	COLOR
0	blue
10	bluish purple
20	purple
30	vermilion
40	red orange
50	yellow orange
60	yellow

If the solutions turn yellow with glucose concentrations of less than 60 mg. per 100 c.c., a dye concentration stronger than 0.1 gm. per 100 c.c. (for example such as 0.11 gm.) should be used. On the other hand, if a glucose solution of 60 mg. per 100 c.c. does not bring about a complete change to yellow, dilution of the dye solution is indicated. One or two trials usually suffice to determine the concentration of the particular batch of dye on hand, which gives satisfactory results.*

TABLE I

COMPARISON OF GLUCOSE DETERMINATION IN LUMBAR CEREBROSPINAL FLUID BY THE INDIGO CARMINE AND SOMOGYI METHODS

NONMENINGITIS PATIENTS		TUBERCULOUS MENINGITIS		MENINGOCOCCUS MENINGITIS		STREPTOCOCCUS MENINGITIS	
INDIGO CARMINE	SOMOGYI	INDIGO CARMINE	SOMOGYI	INDIGO CARMINE	SOMOGYI	INDIGO CARMINE	SOMOGYI
45	41	0	0	10	11	0	0
45	42	0	0	10	15	0	0
45	47	0	7	15	18	0	5
45	56	10	0	15	25	3	0
45	40	10	6	20	11	5	0
50	42	10	8	20	15	10	10
50	53	10	10	25	32	10	11
50	54	10	10	30	30		
50	59	10	11	30	30		
50	60	10	11	30	33		
50	61	15	12	35	36		
55	51	20	11	35	36		
55	67	20	14	40	38		
†60 (or over)	54	20	16	40	46		
60 (or over)	63	20	20	45	39		
60 (or over)	63	25	18				
60 (or over)	68	25	20				
60 (or over)	73	30	21				
60 (or over)	77	30	23				
60 (or over)	86	30	23				
60 (or over)	70	30	27				
60 (or over)	74	30	27				
		30	30				
		30	30				
		30	32				
		35	39				
		40	36				

*The results here reported were obtained with a bottle of dye, stamped "91 per cent pure dye," sold by the National Aniline Company.

†The indigo carmine solution used by us was so adjusted that a yellow color was obtained in all fluids containing 60 mg. or more of glucose per 100 c.c.

THE JOURNAL OF PEDIATRICS
VOL. 8, NO. 1, JANUARY, 1936

CHART 1.

The indigo carmine solution should be freshly prepared about once a month since the dye deteriorates on standing over a long period.

The tints obtained are quite distinctive and are easily reproduced in water color.

The method is accurate to from 5 to 10 mg. per 100 c.c. It is not intended to replace the more exact laboratory methods, but rather to be used when the latter are unavailable or inconvenient. The following comparison of determinations made by the dye method and the Somogyi method will serve to show that differences in the results obtained by the two methods are not of sufficient magnitude to affect diagnostic conclusions (Table I).

REFERENCES

1. Levinson, A.: Cerebrospinal Fluid in Health and in Disease, St. Louis, 1929, The C. V. Mosby Company.
2. Cohn, David J., Levinson, Abraham, and McCarthy, Frances: Am. J. Physiol. 103: 613, 1933.
3. Kasahara, Michio, and Hattori, Shunjiro: Am. J. Dis. Child. 22: 218, 1921.

THE LYSOZYME CONTENT OF BLOOD

WILLIAM L. BRADFORD, M.D., AND JUSTUS B. ROBERTS, M.D.
ROCHESTER, N. Y.

IN 1922 Fleming[1] described a substance widely distributed in the tissues of animals and in plants which possessed a remarkable lytic effect upon certain bacteria. He believed the substance resembled an enzyme; accordingly he named it lysozyme, and the susceptible organism, a micrococcus isolated from the nasal mucous membrane of an individual suffering from coryza, he named *Micrococcus lysodeikticus*.

This lytic substance was demonstrated in the body fluids and in the organs of man. Tears, cartilage, spleen, liver, lung, nasal mucus, sputum, and stomach were found to be particularly active. Blood serum as well as leucocytes contained it, and it was suggested that lysozyme might play an important part in phagocytosis and therefore be possessed of immunologic significance.

Since its discovery this substance has been studied in various clinical conditions. Ridley[2] found that in cases of phlyctenular and of interstitial conjunctivitis the lysozyme content of tears was markedly reduced. In a discussion of the subject Ridley remarked, "The demonstration of a fall in the lysozyme content in disease and of a subsequent rise upon recovery would be very significant. This has been observed in estimation of the lysozyme content of tears, but no work has been done in respect to leucocytes."

Andersen[3] and Findlay[4] each reported a reduction in the lytic power of tears in vitamin A-deficient animals. Findlay observed that no decrease occurred in the activity of blood serum in vitamin A-deficient rabbits. Frank[5] tested the blood serum and saline extracts of liver and kidney in rats and found that only the titer of the liver extracts decreased as a result of lack of vitamin A.

Corper[6] concluded that lysozyme appeared to be of little significance in accounting for organic susceptibility to experimental tuberculosis in the dog and in the guinea pig.

Penrose[7] studied the lysozyme content of saliva in psychiatric patients and concluded that in mental defectives and in dementia precox it was normal, but that it was reduced in organic psychosis, such as general paresis and in parkinsonism.

From the Department of Pediatrics, School of Medicine and Dentistry, University of Rochester.

Kopeloff, Harris and McGinn[8] found no difference between the lytic power of the saliva in postencephalitic patients and in normal persons.

Rosenthal and Lieberman[9] investigated the lytic properties of stools and showed that lysozyme appears in the stools of breast-fed babies more quickly than it does in the stools of those artificially fed. They concluded that lysozyme of mother's milk plays an important rôle in the establishment of the intestinal flora of the newborn.

Recently Hilding[10] reported that the lysozyme content of the nasal mucus was reduced during the course of acute coryza.

Since there is no definite conclusion as yet concerning the immunologic importance of this substance and since it is known to act upon certain pathogenic organisms as well as upon saprophytes, it seemed worth while to investigate its content in normal blood as well as the changes in blood which might occur during acute infections. This report, therefore, deals with the results obtained from such observations.

METHOD

Serums in dilutions ranging from 1 in 5 to 1 in 160 were first studied. Twenty-four-hour growths of *M. lysodeikticus* were washed from agar slants with normal salt solution, standardized to match the turbidity of a No. 9 barium sulphate standard, and preserved with a 1 to 10,000 solution of merthiolate.

In a series of tubes containing diluted serum, equal volumes of the bacterial suspensions (0.5 c.c. serum plus 0.5 c.c. bacterial suspension) were placed. The mixtures were then incubated for twenty-four hours in a water-bath at 37° C. and readings to determine the degree of clearing were made against a blue light. Results were recorded as complete, incomplete, and no lysis.

The study was then extended to an investigation of the lytic substance contained within a given sample of leucocytes. For this purpose 5 c.c. of blood were mixed with 0.010 gm. of potassium oxalate. The blood was centrifugalized, and the leucocyte layer was removed and mixed with sterile distilled water. The number of leucocytes in the first tube was adjusted to 4,000,000 per cubic centimeter. When an equal volume of bacterial suspension was added, the final concentration of leucocytes in the first tube was therefore 2,000,000 per cubic centimeter. Differential cell counts were made by counting 100 cells in smears made from the sample of oxalated blood after staining by Wright's method.

RESULTS

In Table I, showing the effect of dilution and of inactivation of serum upon its lytic activity, the data are arranged in order of greatest lytic effect.

Although too much cannot be implied by stating the percentages in such small groups, certain points are shown by the calculations. First, the serums in scarlet fever, rheumatic fever, and in pneumonia possess similar titers. Second, inactivation appears to have a greater effect upon the lytic principle in the serum of pregnancy than it does in the serum of cord blood. The differences in the effect of dilution and of heat upon the serums in the latter two conditions constitute an interesting point for further investigation.

TABLE I

EFFECT OF DILUTION AND OF INACTIVATION UPON THE LYSOZYME CONTENT OF BLOOD SERUM

	NO. CASES	DILUTION OF SERUM PER CENT SHOWING COMPLETE LYSIS				
		1:5	1:10	1:20	1:40	1:80
Serum Not Inactivated						
Pregnancy	11	100	36	27	0	0
Cord blood	33	85	70	26	9	0
Rheumatic fever	5	60	60	40	20	0
Scarlet fever	17	41	36	12	0	0
Pneumonia	8	38	25	0	0	0
Normal children	9	33	22	22	0	0
Serum Inactivated 56° C. for 30 min.						
Congenital lues	14	21	0	0	0	0
Cord blood	33	15	12	9	3	0
Diabetes	22	0	0	0	0	0
Pregnancy	19	0	0	0	0	0
Cancer	6	0	0	0	0	0

From Chart 1 it is evident that leucocytes taken at the height of scarlet fever, rheumatic fever, measles (complicated), cervical adenitis, and after artificial fever therapy were definitely active. In whooping cough and in lymphatic leucemia they were less active. In lobar pneumonia a marked decrease in their lytic principle was observed after the crisis occurred.

From data available concerning the nine normal persons, it is possible to estimate the comparative lysozyme activity of leucocytes and of serum in these cases. The average leucocyte count in seven of the nine was 8,040 per cubic millimeter. One cubic centimeter of blood would therefore contain 8,040,000 leucocytes. In Chart 1, the average leucocyte content (in the normal cases) which caused complete lysis was 235,000 per cubic centimeter. By liberating the entire lysozyme content of the leucocytes in 1 c.c. of plasma, complete lysis should occur in a dilution of $\frac{235,000}{8,040,000}$ or 1:33 on the average.

With the serum in three of the nine normal children, complete lysis occurred at 1:5 dilution, or rather at 1:10 dilution when the equal volume of bacterial suspension had been added. Upon this basis, therefore, complete lysis occurred at the average for the nine cases

at a dilution of 1:3. Therefore, the lysozyme content of the leucocytes would be $\frac{33}{3}$ or 11 times that of serum.

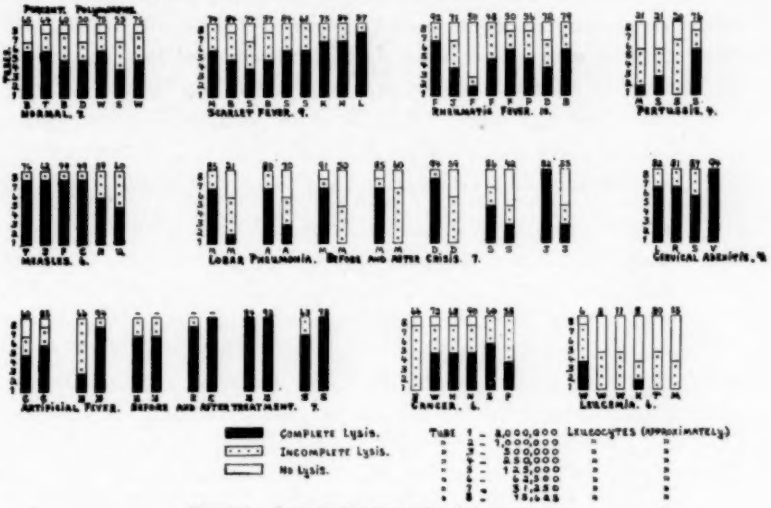

Chart 1.—Lysozyme content of leucocytes.

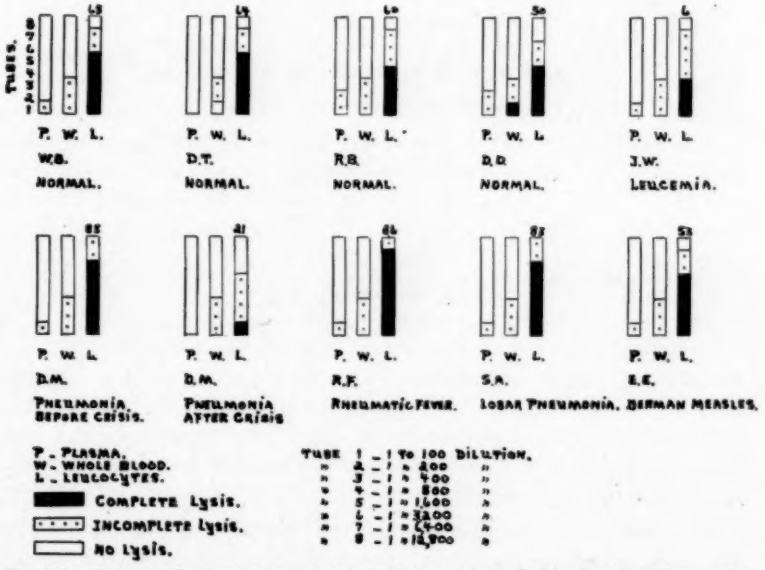

Chart 2.—Comparative lysozyme content of plasma, of whole blood, and of leucocytes.

It is interesting that Ridley[2] using a different method observed that whole blood into which the lysozyme content of the leucocytes had

been liberated by freezing contained 32 units of lysozyme as compared with 5 units of serum, a ratio of approximately 6 to 1.

Chart 2 further illustrates the results when comparative tests were made on plasma, the whole blood, and the leucocytes of ten individuals. In each case it is evident that the plasma was least active and the leucocytes were most active in the production of lysis.

Tabulation of the results obtained with 95 leucocyte suspensions indicates that there was a direct correlation between the lytic activity and the percentage of polymorphonuclear leucocytes in the suspension.

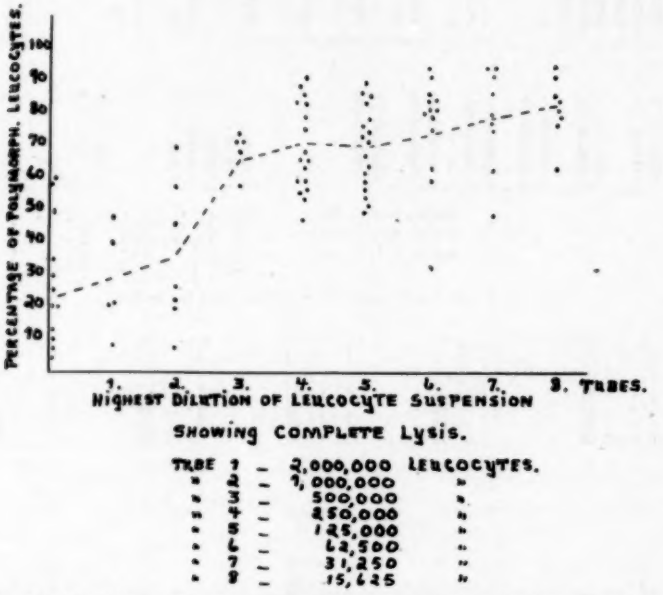

Chart 3.—Relationship of the lysozyme content of leucocytes to the percentage of polymorphonuclears.

In Chart 3 the dotted line passes through the average of the percentages of polymorphonuclears, and the group of dots at the left-hand end of the line represents suspensions in which no lysis occurred. Differential counts indicated as shown in the chart that the more active suspensions usually contained the highest percentage of polymorphonuclear leucocytes.

This was further confirmed when the titer of a pleural exudate (91 per cent polymorphonuclears) produced in a rabbit with aleuronat was compared with that of one produced with a beef extract acacia mixture (30 per cent polymorphonuclears) and with a phosphorous peritoneal exudate from a guinea pig (10 per cent polymorphonuclears).

In the case of the aleuronat exudate, complete lysis resulted in the fourth tube (250,000 leucocytes), whereas in the beef extract acacia exudate and in the phosphorous exudate lysis was not complete even in the first tube (2,000,000 leucocytes).

DISCUSSION

In these experiments the term lysozyme has been applied to the lysis-producing substance in the material tested. It is admitted that other lytic substances besides lysozyme may have played some part in the dissolution of the bacterial suspensions. In the case of serum, bacteriolysins specific for the organism used may have been present while in the leucocytes certain nonspecific substances such as leukins or β lysins may have played a part. Attempts to obtain purified material from blood according to the method of Wolff,[11] however, failed. Moreover, the purpose of the experiments was comparative.

In view of the great activity exhibited by leucocytes, particularly those of the granular series, it would be of considerable interest to know if the lytic effect of such substances as nasal mucus, saliva, and milk upon such a susceptible organism as *M. lysodeikticus* depends upon the leucocyte content of the material.

Since the bactericidal power of blood depends to a great extent upon the leucocytes[12] and since the lysozyme content of blood also is greatest in them, it is interesting to think of the possible rôle this substance might play in resistance against bacterial invasion. Fleming[13] has suggested that in gonorrheal pus the ordinary healthy leucocyte rapidly dissolves the gonococcus after phagocytosis and suggests that those cells which contain undissolved organisms may be deficient in such substances as lysozyme.

Meyer and his associates[14] recently stated that "lysozyme is an enzyme or enzyme mixture which splits a reducing substance from certain mucoids and from the polysaccharides derived from them." Such a substance contained in leucocytes might naturally be of importance in the mechanism by which these cells resist bacterial invasion.

SUMMARY

The lytic effect of serum, plasma, whole blood and of leucocytes upon a susceptible organism (*Micrococcus lysodeikticus*) has been studied.

The lysozyme titer of serum in acute infections did not differ greatly from that in normal individuals.

When comparative tests of plasma, whole blood, and leucocytes were made in a group of cases, plasma was found to be least active while leucocytes possessed the greatest activity. In certain acute in-

fections and after artificial fever, the lytic power of the leucocytes was found to be increased. It was decreased after the crisis in pneumonia.

In normal control subjects and in children during acute infections, the lysozyme content of the leucocytes seemed to be increased or decreased in direct relationship to the percentage of the polymorphonuclear cells.

REFERENCES

1. Fleming, A.: Proc. Roy. Soc., London. Series B, 93: 306, 1922.
2. Ridley, F.: Proc. Roy Soc. Med. 21: 1495, 1927, 1928.
3. Andersen, O.: Acta paediat. 14: 81, 1932-1933.
4. Findlay, G. M.: Brit. J. Exper. Path. 6: 16, 1925.
5. Frank, M.: Monatschr. f. Kinderh. 60: 345, 1934.
6. Corper, H. J.: Am. Rev. Tuberc. 25: 59, 1932.
7. Penrose, L. S.: Lancet 2: 689, 1930.
8. Kopeloff, N., Harris, M. M., and McGinn, B.: Am. J. M. Sc. 184: 632, 1932.
9. Rosenthal, L., and Lieberman, H.: J. Infect. Dis. 48: 226, 1931.
10. Hilding, A.: Arch. Otolaryng. 20: 38, 1934.
11. Wolff, L. K.: Ztschr. f. Immunitätsforsch. u. exper. Therap. 50: 88, 1927.
12. Boys, F., and Gunn, F. D.: Proc. Soc. Exper. Biol. & Med. 32: 27, 1934.
13. Fleming, A.: Proc. Roy. Soc. Med. 26: 1, 1932.
14. Meyer, K., Thompson, R., Palmer, J., and Khorazo, D.: Science 79: 61, 1934.

THE SIGNIFICANCE OF INDIVIDUAL VARIATIONS

ALFRED H. WASHBURN, M.D.
DENVER, COLO.

THE purpose of this report is the presentation of a point of view. Such scientific data as may be given are displayed merely to illustrate and, if possible, to enforce this point of view. It might have been wiser to choose simply the title, "Individual Variation." For I am raising rather than answering the question of the significance of individual variations in the estimate of so-called "normal" growth in infancy and childhood.

It is an accepted dictum that a familiarity with the "normal" is necessary before one can recognize the "abnormal." Thus an x-ray of the heart is of no value in the diagnosis of cardiac disorders unless we know what the appearance of the "normal" heart may be in an x-ray picture. Similarly a leucocyte count would be of small value in aiding us to diagnose pneumonia, appendicitis, or whooping cough, if we did not know what the "normal" leucocytic picture might be.

But what is this thing which we call "normal"? To borrow a phrase from the annual report of one of our large foundations, what is "that elusive moving average which the layman with blithe indifference to the complexity of the concept calls normal growth"? Two children may be strikingly different in the development of such widely separated structures as the jaw and the heart, or in such varied functions as are portrayed by the electrocardiogram and the basal metabolism determination and yet be equally healthy so far as we can tell. Thus we know that it is not possible to select a single "norm" and claim that every departure from it represents disorder of some sort. Averages of many figures for everything from the child's weight to the number of red blood cells are equally unreliable as criteria for establishing the presence or absence of disease. To be sure, gross deviation from the average will point ordinarily to the presence of disease but, all too frequently, we are unable to say which minor deviations are merely the variations above and below the average line which went to make up the average figure and which ones represent the result of some disease process which is just starting. Moreover, average figures alone tend not only to hide the very picture we need of the degree of difference between individuals, but also to obliterate

From the Child Research Council and the University of Colorado School of Medicine.

Read at the Forty-Second Annual Meeting of the American Pediatric Society, Cleveland, May 3, 1935.

almost completely the character of the changes and variations in any one individual as he progresses from birth to maturity.

The building up of so-called "normal standards," then, must represent something more than the calculation of averages if it is to be of maximum service to us in the diagnosis of disease. It must consist in the delineation of a "health zone"—a zone within which variations may run from one edge to the other without indicating the presence of disease but outside whose borders variations may not extend without pointing definitely to disorder. Into this zone must be built also a picture of the possible extent of variation for any one individual during the changes incident to growth and development, as compared with the maximum extent of the whole zone for all children. And eventually we may hope, perhaps, for the time when we can paint into this picture the criteria which will enable us to say whether a given child—say Jack or Jill—should show wide or narrow fluctuations within the zone, and whether their individual variations may be expected to lie in the upper, middle, or lower portion of the zone.

Such normal standards of the future should show these zones of healthy variations for every part of the growing child which can be visualized directly or indirectly. They should also depict the same sort of zones for all the measurable functions of the growing human organism during its years of change.

The Child Research Council of Denver has set itself the task of building up some of these zones of healthy variation in various structures and functions of the growing human organism. It is attacking this problem by studying a group of children, representing a rough cross-section of Denver's population, from birth to maturity. Each child is being studied periodically from as many different aspects as the size and interests of our staff of forty can encompass.

The few illustrations which I shall show you now are all taken from some one or other of these Child Research Council studies. Since our institution is still in its infancy, I should not wish any one in my audience to assume that I am presenting this material as representative of the whole zone of individual variation in relation to any one group of findings. They merely illustrate a little of the extent and character of these individual variations and suggest methods for depicting them.

The first pictures (Fig. 1) represent the sort of individual difference with which we are so familiar that it is taken for granted. In our studies we attempt to translate our rough impressions into some sort of objective record which will be both measurable and permanent. Here we have accurate profile photographs, taken to scale, of two children of the same age. Although some of the striking differences

are, of course, dependent upon sex, many others are quite unrelated to the fact that one happens to be a boy and the other a girl. I should like to call your attention particularly to the characteristics of the lower face and jaws of these two youngsters.

In the next illustration (Fig. 2) are shown photographs of accurate casts of the teeth of these two children shown in Fig. 1. Even the

Fig. 1.

Fig. 2.

Fig. 3.

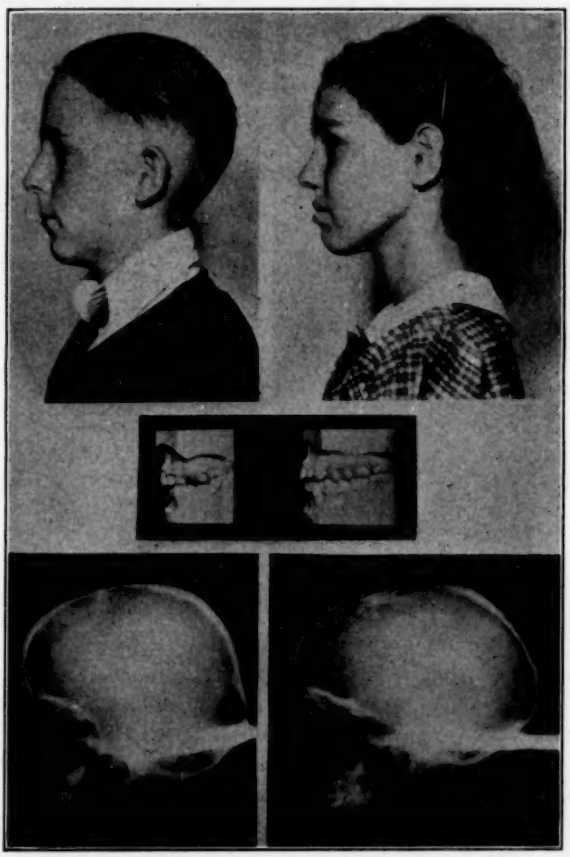

Fig. 1.—Profile photographs of W. J., a boy eleven and one-half years old, and C. S., a girl of the same age. Note the difference in jaw development.

Fig. 2.—Plaster impressions of W. J. (left) and C. S. (right) made at the same age as the photographs shown in Fig. 1. Note the striking differences in development of the teeth.

Fig. 3.—Lateral roentgenograms of head of W. J. (left) and C. S. (right) made at the same age as photographs and impressions (Figs. 1 and 2).

most superficial inspection shows striking differences in the development and contour of these jaws. Such differences may be measured in three dimensions, recorded and studied year by year as these chil-

dren grow and develop from early infancy to maturity. By repeating the same process on 100 children the zone of individual variation may be constructed slowly but surely.

In Fig. 3 are reproduced the lateral head roentgenograms of these same two children. By means of these x-ray pictures combined with anteroposterior x-ray pictures, all taken in the same relative positions, one can visualize and measure the fundamental underlying structures which are responsible for the variations already noted. In serial roentgenograms of this sort, taken each year on a group of children, one can study the component parts of the development of the face and jaws as they grow, and thus analyze the differences between individuals.

These three figures, then, illustrate two points: first, the simple picture of variation in structures; and second, a method for accurate objective study of the differences in growth and development from birth to maturity in two or more children.

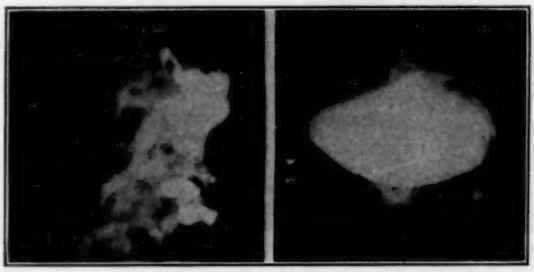

Fig. 4.—Visualization of the stomachs of two healthy babies of the same age and size, following the ingestion of approximately equal amounts of formula and barium. This illustrates the extremes of individual variation.

The next two films (Fig. 4) illustrate the unusual amount of difference sometimes encountered in one single examination of two infants. These two roentgenograms were taken of two babies of about the same age and size and at the same time interval following the ingestion of their regular formula to which barium had been added. It may be noted that a large portion of the barium meal in the one baby has already moved along into the small intestine while in the other most of the meal is still in the stomach, which seems quite enormous. We see here an illustration of individual variation which involves both structure and function.

In the next illustration (Fig. 5*A*) is seen not the hearts of two different children but roentgenograms of the same child in the supine (left) and in the upright positions. I should like to have you compare this situation with that shown in the next picture (Fig. 5*B*). Here we see chest roentgenograms of another healthy child taken, as

before, both in supine and upright positions. No appreciable change is noted in the shape of the heart. It may be interesting also to compare two things in this child's chest with the same findings in the first child—note the shape of the heart and the heaviness of the shadows cast by the bronchi and pulmonary vessels. We may interpret Figs. 5*A* and *B* as illustrating two points: first, that the differences in structures are not just skin deep but include also the essential internal organs; and second, that these differences involve not merely the form of that structure but also its response to changes in environmental conditions. As one is confronted with more and more data of this sort, one becomes increasingly impressed with the complexity of this

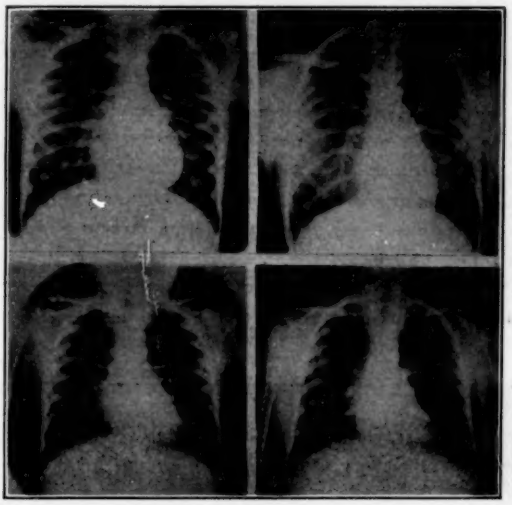

Fig. 5*A*.—Chest roentgenograms of W. M. in supine (left) and upright position, showing marked alteration in heart shape with change in posture. Note also relatively heavy "lung markings."

Fig. 5*B*.—Chest roentgenograms on M. L. in supine (left) and upright position. Contrast the absence of change in heart shape and the relatively light "lung markings" with these same findings in W. M. (Fig. 5*A*).

concept of the so-called "normal." For what is normal for one child —e.g., a heart which shows no change with a shift in position—is not at all normal for the other child. This situation is even more striking in view of the fact that the heart is one organ whose shape and general contour, as shown on serial x-ray plates, changes remarkably little from early infancy to adolescence.

The next three illustrations depict the same type of picture of variations, but this time in the realm of function rather than of structure. Fig. 6 shows selected tracings of the respiration of four healthy babies within the same age period of three to six weeks, and all taken during

apparently quiet sleep. Some babies may show a shift from the smooth even type of breathing shown in the top tracing to the markedly periodic type shown in the third tracing within one brief period of observation. Even in the portrayal of one fairly simple function, then, we still find our expected picture of variation both in one individual and between different individuals.

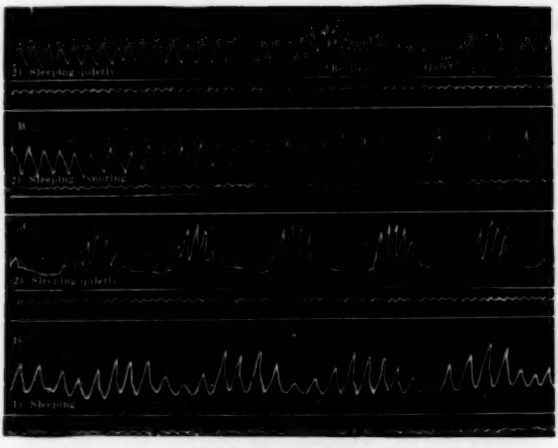

Fig. 6.—Tracings of the respirations on four healthy infants showing marked individual differences.

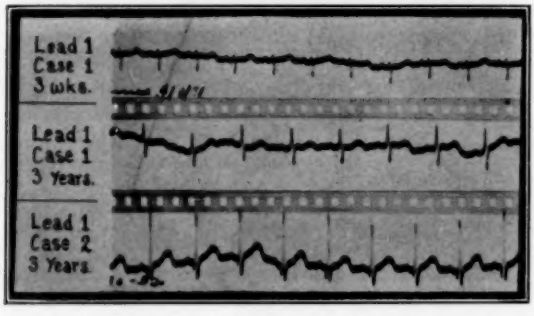

Fig. 7.—Electrocardiograms showing variations in the findings on one individual at different ages and variations between two individuals of the same age.

In the second of this group (Fig. 7) I have tried to demonstrate the presence of a similar picture which will be found when we try to obtain a permanent record which will portray cardiac function. The upper two tracings are taken on the same child at the ages of three weeks and three years. The lowest tracing is from a different child in our group of healthy youngsters—also at the age of three

years. No intricate knowledge of electrocardiography is needed to see that each of these tracings is strikingly different from the other two.

Another rather complex picture is presented by charting the results of 411 basal metabolism determinations on eighty-one children, between the ages of two and twelve years (Fig. 8). However, I believe it illustrates unusually well the stretching out of a health zone within which individual variations are seen to be quite marked as between different children and definitely less marked, but still present, over a given time in any one child. It also shows a definite difference between the sexes and the tendency for the rate on any one child to stay, roughly, in the same general part of the large zone. To bring out this latter point I have sketched in the curves for 6 different children—three boys and three girls—covering the whole age period which is depicted.

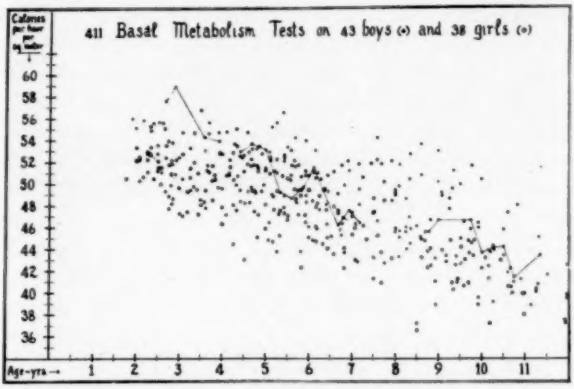

Fig. 8.—Individual variation in basal metabolic rates illustrating: the wide zone of healthy variation between different children of the same age; the fluctuations in six individual children in successive tests; the difference between the sexes; and the tendency for any one individual's rates to remain in the upper middle or lower portion of the zone.

The constant repetition of this experience of finding marked individual differences, no matter what part or function of the growing child was being studied, has stimulated me to present this brief report. I realize that there is nothing new or original in the concept, but I feel that it deserves greater stress in these days of standardization. It would seem that the first step in reaching an understanding of just what healthy growth and development really is must be the delineation of the whole range of possible variation during health in every part and function of the child. The longitudinal study of the individual child, from as many different aspects as possible, at regular intervals, and throughout the period of growth, appears to be a logical method of approach to the problem.

CONGENITAL SHORTENING OF THE ESOPHAGUS

JAMES B. GILLESPIE, M.D.
URBANA, ILL.

FINDLAY and Kelly[1] in 1931 described an anomaly that was characterized by congenital shortening of the esophagus and by the presence of a portion of the stomach in the thoracic cavity with stenosis at the junction of the esophagus and thoracic stomach. In 1934 Clerf and Manges[2] reported fourteen similar cases. Monkhouse and Montgomery[3] have used the term "partial thoracic stomach" in reporting seven cases of short esophagus of mild degree. There have been many articles published on congenital diaphragmatic hernia or hiatal hernia without mention as to whether the esophagus was long or short. Le Wald[4] does not mention the esophagus in his classification of certain congenital and acquired conditions of the diaphragm.

The short esophagus presents at times interesting and complex sets of symptoms. Prior to the use of roentgenography, hernia of the diaphragm was diagnosed infrequently. Manges and Clerf[5] stressed that if complete roentgen ray studies of the esophagus as well as the stomach had been made in all reported cases of diaphragmatic hernia, so called, many would be listed as cases of congenitally short esophagus. They believe that the terms "hernia of the diaphragm" or "hiatal hernia" are misleading since, due to faulty development of the esophagus, the portion of the stomach found above the diaphragm has never been in the abdomen. Consequently, the abnormality is not a hernia in the true sense.

The essential points in the roentgen ray diagnosis of congenital shortening of the esophagus are: First, a portion of the cardiac end of the stomach must be shown to stay above the level of the diaphragm. Second, the esophagus must be shown to be too short to reach as low as the level of the diaphragm. Roentgenographically, the cases of Clerf and Manges have shown some narrowing where the esophagus joins the stomach. In the few reported cases of short esophagus examined esophagoscopically, fairly constant findings were recorded. These consisted of a short esophagus, narrowing of the esophagogastric junction, finding a portion of the esophagus lined by gastric mucosa, and the absence of the normal hiatus esophagus. Ulceration, usually at the junction of the esophagus and stomach, has been found in a number of cases.

No typical symptom group has been suggested. Monkhouse and Montgomery recognized two groups: (1) those with dysphagia and (2) those without dysphagia. Dysphagia and regurgitation with dis-

From the Department of Pediatrics, Carle Hospital Clinic.

turbance in nutrition and growth may occur. Certain cases are probably symptom free and are discovered only by chance in adult life. Cardiorespiratory and gastrointestinal symptoms have been reported. Harrington[6] reported the occurrence of pain which may be referred to the left shoulder and radiate down the arm. This was ascribed to spasm of the diaphragm. In cases in which the esophagus is short and the stomach fixed and irreducible, this symptom would seem unlikely.

Reported herein is a case of congenital shortening of the esophagus with a large portion of the stomach lying within the thoracic cage. The patient was free of symptoms relative to this condition, and it was discovered incidentally during the course of a routine general

Fig. 1.—The short esophagus enters the uppermost cardiac portion of the stomach. Approximately one-half of the stomach lies within the thoracic cavity.

examination. Fig. 1 shows the congenitally short esophagus and partial intrathoracic stomach noted at the time of the first examination.

The patient, a girl, was twelve years old. She was first seen Feb. 13, 1935. The father and mother were alive and well. There were three other children, one of whom had congenital heart disease. The patient had had measles, chickenpox, and mumps. At nine years of age she had bronchopneumonia. She had not begun to menstruate. Tonsillectomy and adenoidectomy were performed at four years of age following numerous attacks of tonsillitis. She had been a full-term baby, delivered normally, and weighed 7 pounds. Development had been normal. For two months prior to Feb. 13, 1935, she had been very nervous, afraid at night, and irritable. She could not go to sleep readily at night. On February 12 she nearly fainted several times but complained of nothing else. There were no symptoms referable to the gastrointestinal or genitourinary tracts.

She was a tall, thin, sickly looking girl. Her eyes were puffed, and her features were heavy and myxedematous in type. She cried easily. Her weight was 91 pounds (41.3 kg.); her height was 65.25 inches. Average weight for her age is 121 pounds (55 kg.). The blood pressure was 115 systolic and 80 diastolic; the pulse rate was 108; and the temperature was 98.4° F. She had excellent teeth. There were bilateral infected tonsil tags and evidence of old rachitic changes in the chest wall. The heart and lungs were negative. There was no abdominal tenderness; the liver, spleen, and kidneys were not palpable. She had a marked dermatographia. Examination of the blood revealed: hemoglobin, 82 per cent; erythrocytes, 4,060,000; and leucocytes, 8,300, of which 37 per cent were lymphocytes, 0.5 per cent monocytes, 60.5 per cent neutrophiles, and 2 per cent eosinophiles. Three urinalyses were negative. The blood Wassermann and Kahn tests were negative. The basal metabolic rate was plus 5 per cent. The Mantoux test with 0.1 mg. of old tuberculin was negative. Roentgenograms of the head and wrists were negative. Roentgenogram of the chest showed about one-half of the stomach lying in the thoracic cavity, and the heart shadow displaced to the left. Roentgenographic and fluoroscopic studies of the stomach showed a short esophagus and a large portion of the stomach lying above the diaphragm. Studies with the patient both standing and lying down showed an entire absence of tortuosity of the esophagus. No stenosis at the esophagogastric junction or ulceration of the esophagus was noted. Esophagoscopic studies were not made. The fluid intake and output were within normal limits.

She was placed on a high vitamin, high caloric diet, and a régime of rest was outlined. Small doses of phenobarbital were given. There was a prompt improvement in her general condition and a progressive gain in weight. She gained 18 pounds (8.1 kg.) in four and a half months. On June 1, 1935, she weighed 109 pounds (49.5 kg.) and was subjectively well. She has returned for frequent check-ups and has reported no recurrence of the nervousness, irritability, or fainting spells.

On the whole, congenital shortening of the esophagus with thoracic stomach resulting therefrom is not a frequently diagnosed condition. In all cases of supposed diaphragmatic hernia, steps should be taken to determine the length of the esophagus. The absence of stenosis at the esophagogastric junction and complete absence of any symptoms, referable to the anomalous condition in this case, are rare. If this condition is to be viewed in the light of a diaphragmatic hernia or hernia of the stomach through the diaphragm, the term "congenitally fixed" or "congenitally irreducible" should qualify the term "hernia." Surgically it is important to differentiate shortening of the esophagus with resulting partial or complete intrathoracic stomach from simple herniation of the stomach into the thoracic cavity. This last condition in many cases is amenable to surgical treatment, while a markedly short esophagus makes successful surgical repair extremely unlikely.

REFERENCES

1. Findlay, L., and Kelly, A. B.: J. Laryng. & Otol. 46: 797, 1931.
2. Clerf, L. H., and Manges, W. F.: J. A. M. A. 102: 2008, 1934.
3. Monkhouse, J. P., and Montgomery, S. K.: J. Laryng. & Otol. 48: 743, 1933.
4. Le Wald, L. T.: Am. J. Roentgenol. 20: 423, 1928.
5. Manges, W. F., and Clerf, E. H.: Am. J. Roentgenol. 33: 657, 1935.
6. Harrington, S. W.: J. A. M. A. 101: 987, 1933.

THE PROLONGED USE OF ACETYLSALICYLIC ACID WITH THE ADDITION OF MAGNESIUM OXIDE IN THE TREATMENT OF RHEUMATIC INFECTION IN CHILDREN

ALBERT D. KAISER, M.D.
ROCHESTER, N. Y.

CERTAIN rheumatic manifestations, especially those involving the joints and muscles, are usually relieved by the administration of sodium salicylate, acetylsalicylic acid, or some other similar drug. Though relief may be obtained from any of these drugs, they may produce unpleasant symptoms in some children and for that reason are not generally administered over a long period of time.

Inasmuch as rheumatic infections in children are likely to be of long duration or recurrent in their course, it seemed desirable to observe the influence of a so-called antirheumatic drug when used over a long period of time. Relatively few reports are available on the prophylactic value of drugs in the treatment of the rheumatic child. Leech[1] studied a group of sixty-seven children with inactive or potential rheumatic heart disease. These children were given daily doses of 20 grains of acetylsalicylic acid for six months. A control group with similar lesions was also used. He found in general that there were fewer recurrences of chorea in the experimental group than in the control group. The control children did not do as well in the matter of gain in body weight, improvement in heart rate, general bodily comfort, and actual physical capacity as judged by a functional classification based on the ability to carry on normal activities without discomfort. More recently Podolsky and Goldstein[2] made a similar study and concluded that acetylsalicylic acid probably exerts a prophylactic influence on the rheumatic syndrome in children.

Various drug preparations have been employed in the treatment and in the prophylaxis of rheumatic disease. The salicylates are looked upon as the sovereign remedy, but the mechanisms by which they bring about the therapeutic success in the toxic state remain obscure. Birkhaug[3] suggested that its therapeutic success is effected by weakening the pathogenic microorganisms and their capacity to secrete the deleterious exotoxins.

Recent papers have indicated that magnesium exerts a definite synergic effect when given in combination with certain antipyretics,

From the Department of Pediatrics, the University of Rochester School of Medicine and Dentistry.

e.g., sodium salicylate, acetylsalicylic acid, cinchophen, and amidopyrine. Winter and Barbour[4] showed that such combinations have also shown uniformly a lower toxicity than would be predicted from the known toxicity of their individual components. Experimental and clinical studies agree that the addition of magnesium oxide potentiates the early antipyretic effect of acetylsalicylic acid. Potentiation occurs when two drugs have different points of attack in the cell. Winter and Richey[5] showed that acetylsalicylic acid increases gastric acidity. When magnesium oxide or chloride is added to the acetylsalicylic acid, normal gastric acidity may be more nearly maintained. Simon[6] showed that the symptoms of gastric irritation following the oral administration of acetylsalicylic acid are practically eliminated by the addition of magnesium oxide.

Inasmuch as the drug selected for this clinical study* was to be used regularly over a long period of time, the one likely to produce the least gastric disturbance was selected. The use of acetylsalicylic acid with the addition of magnesium oxide seemed from the experience of others to be best suited for this purpose. Accordingly a preparation containing 3 1/3 grains of acetylsalicylic acid and 3 1/3 grains of magnesium oxide was used. Such a preparation appears to be equivalent grain for grain to acetylsalicylic acid alone.

Because of the protean nature of rheumatic disease, it seemed essential to select children in the treated and in the control groups who presented comparable complaints; otherwise no conclusions could be drawn on the influence of any drug administration. Seventy-five children with an average age of eight years and nine months were selected for the daily administration of acetylsalicylic acid with magnesium oxide; an equal number whose average age was eight years and two months served as controls. In a general way the specific rheumatic complaints were as much alike in the two groups as it was possible to select the cases. The period of observation was alike for the two groups as to both duration and season. Four types of cases were considered, each child being placed in one of these classes. The first class consisted of those who presented manifestations of arthritic or muscular pains only. In both the treated and the control groups there were thirty-one children in this class. The second class included those who in addition to arthritic or muscular pains showed definite evidence of rheumatic carditis. There were twenty-seven children in each group, treated and control, with such complaints. Sixteen children with chorea only, eight of whom received the drug while an equal number were untreated, made up the third class. Also included in the study were nine children with chronic rheumatic carditis who received the drug and nine who did not receive it. About one-half of the children were

*This study was made possible by a grant from the Calco Chemical Company, Bound Brook, N. J.

clinic cases, while the remainder were taken from private practice. The children represented, therefore, a cross-section of the child population in a community where rheumatic infection has an average incidence for the Eastern Atlantic states.

All children utilized in this study were examined, and detailed histories of their rheumatic complaints were listed. Monthly reexaminations were made throughout the period of observation, and in many instances the reexaminations were more frequent. The treated children received from 10 to 15 grains of acetylsalicylic acid with magnesium daily, the dosage depending on the age of the child and the nature of the complaints. The drug was given in tablet form which caused the children no trouble in most cases. Since the drug was supplied free of charge to the patients, better cooperation of the parents was assured. In the case of a few children the parent admitted failure to insist upon the regular administration of the drug, particularly when the child was feeling perfectly well. In the great majority of the cases the drug was taken faithfully. The period of observation for most of the cases was one year, in the remaining cases nine or six months. The clinical estimate of the child's condition was obtained from examination of the child by the same physician throughout the entire period, from the parent's report on the child's complaints, and from reports of others familiar with the child, such as the teacher or the school nurse.

Since the children in the control group presented the same types of rheumatic manifestations as those in the treated group and since they lived in the same localities and in approximately similar social surroundings, it was felt that comparison of the treated children with the control children fulfilled the usual requirements for a comparative clinical study. The follow-up social work and the medical examinations were carried on throughout the year by the same staff in the cases of both the treated and the control groups.

No attempt was made to draw any conclusions as to the effect of the drug on any child until the allotted period of observation, which was twelve, nine, or six months, had been completed. At that time a summary of the progress of each individual child was made and a statistical study was undertaken of the outcome of each child in the group treated with the daily administration of acetylsalicylic acid with magnesium and in the control group who did not receive the drug.

There were among the seventy-five treated children under observation thirty-one who complained of arthritic or muscular pains only. Most of these children had other signs of a rheumatic infection, such as pallor, fatigue, anorexia, and in some instances headache, frequent nosebleeds, and occasional abdominal or pleuritic pains. They did not, however, reveal any anatomic evidence of cardiac involvement or

show any signs of chorea. They were brought to the physician or to the clinic because of the discomfort associated with prolonged or recurrent attacks of pain, which in each instance was considered to be of rheumatic origin. The duration of the rheumatic pains prior to the period of observation was not exactly alike in the treated and in the control groups. There were somewhat more children in the control group who had their first complaint of pain prior to the beginning of this study. Nearly comparable numbers had complained of arthritic pains for a period of from one to five years preceding the start of the period of observation. Children subject to arthritic pains do not have them continuously, but careful questioning will reveal the fact that the pains may recur from time to time and are especially likely to cause the child to complain in the fall and in the winter months.

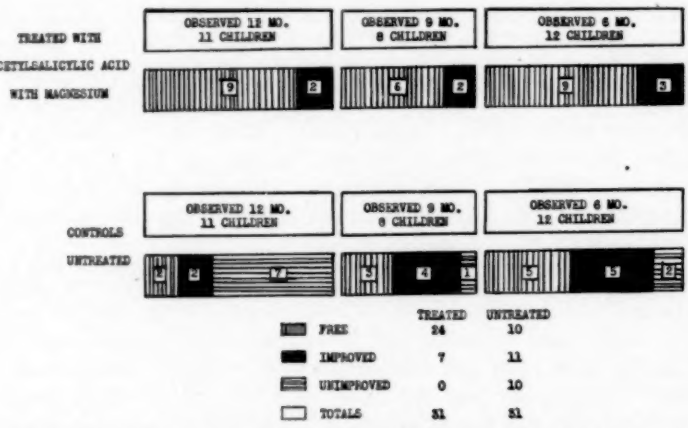

Chart 1.—Results in rheumatic children with manifestations of arthritic or muscular pains only.

In summarizing the course of a child's complaints at the close of the period of observation, the end-result was listed either as free from the complaint for which the treatment was instituted, as improved, or as unimproved. As noted in Chart 1, twenty-four of the thirty-one children receiving a daily ration of acetylsalicylic acid with magnesium were free from their complaint at the end of the short or long period of observation, while among the thirty-one children who did not receive the drug only ten were free from their complaints. Improvement was noted in children from both groups, but among the untreated or control children there were ten who showed no improvement in their condition throughout the entire period of observation. The combined estimate of the child by the parent, the social worker, and the physician seemed to confirm the opinion that children suffer-

ing from arthritic or muscular pains were definitely benefited by the daily administration of small amounts of acetylsalicylic acid with magnesium.

When carditis, either of recent origin or of long standing, is associated with rheumatic pains, the value of any drug administration is not clearly evident. The cardiac involvement in the fifty-four children considered in this class was well compensated, for the children in both the treated and the control groups were all able to be up and about although many of them were either in a convalescent home or on a modified schedule at their own homes. The duration of the carditis was somewhat more recent in the control children, but in general the two groups were similar. As noted in Chart 2 no appreciable difference is evident in the end-results of the two groups when the com-

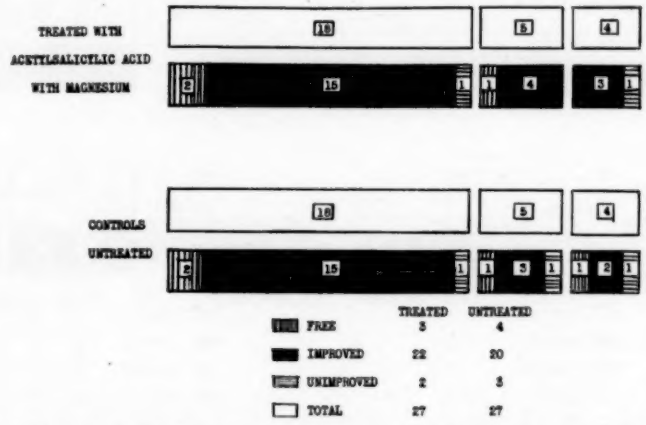

Chart 2.—Results in rheumatic children with manifestations of pains and carditis.

bined rheumatic manifestations are considered. An analysis of the symptoms separately showed that 91 per cent of the treated patients were relieved of their arthritic pains, while 65 per cent of the control patients were relieved over the same period of time. The cardiac condition, however, as noted on physical examination and as determined by functional testing, remained unchanged in most of these children. Anatomically ten children out of the fifty-four showed a change in the physical examination of the heart. The murmur had disappeared in these ten cases, the majority of which were in the control group. The daily administration of acetylsalicylic acid with magnesium oxide brought some comfort to a number of children suffering from arthritic pains and carditis, but as far as we could detect had no unusual beneficial effect on the endocardial involvement in these children.

There were sixteen children with chorea under observation, eight receiving acetylsalicylic acid with magnesium regularly and the remainder untreated or receiving some other type of medication. It was the first attack of chorea in two of the treated children and in four of the control children, the other children in both groups having had at least one previous attack. At the close of the observation period five of the treated children were free from chorea, and three showed definite improvement; while among the control children two were free from chorea, five were improved, and one remained unimproved. These sixteen cases were considered definite clinical cases of chorea with no other rheumatic manifestations. The number under observation was too small to permit any conclusions as to the results of the therapy, but it must be admitted that the children who received

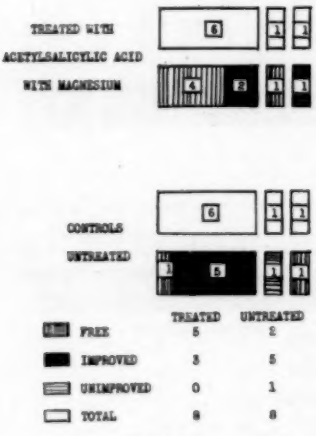

Chart 3.

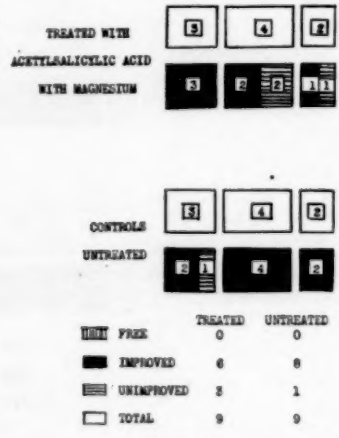

Chart 4.

Chart 3.—Results in rheumatic children with manifestations of chorea.
Chart 4.—Results in rheumatic children with manifestations of carditis alone.

acetylsalicylic acid with magnesium fared better than those who received no medication or who received varying amounts of phenobarbital.

In order to ascertain the effect of the daily administration of acetylsalicylic acid with magnesium on children who have evidence of rheumatic carditis but no other manifestations, nine children in each group were considered. With the exception of two children in each group, the carditis was known to be present for more than two years. When these children were placed under observation, they were free from any cardiac decompensation and were either up with normal activity or in a convalescent home. The improvement of these children was determined chiefly by the change noted in the physical examination of the

heart at the beginning and at the end of the period of observation. As noted in Chart 4 no advantage could be seen for the treated group. In no child of either group did the murmur disappear. The control children actually showed a somewhat greater improvement than the treated children as far as the anatomic lesion of the heart is concerned. Among the treated cases there was no child who developed an attack of decompensation, while one child in the control group had such an attack. A year's observation on children with cardiac disease is insufficient to warrant any conclusions. It seems improbable that the daily administration of 10 or 15 grains of acetylsalicylic acid with magnesium oxide had any measurable beneficial effect on those children who have evidence of rheumatic carditis and no other rheumatic manifestations.

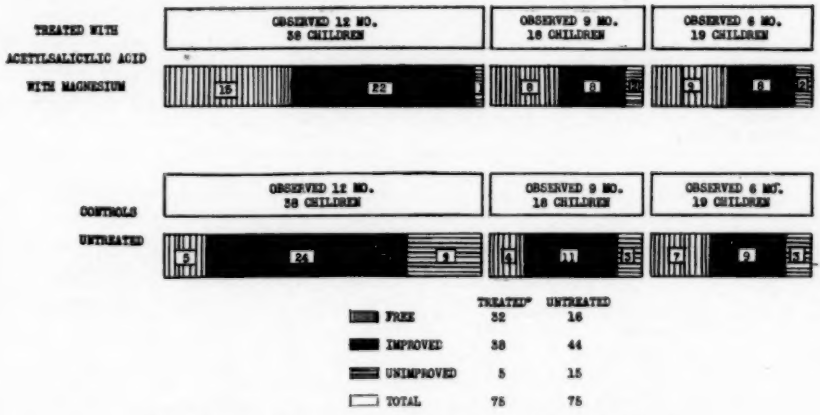

Chart 5.—Results in rheumatic children. All cases studied.

As noted in Chart 5 in which all the rheumatic children are included regardless of the type of manifestation, those children treated with acetylsalicylic acid with magnesium on the whole fared better than those not so treated. If it were not for the fact that somewhat similar children were selected for this study at the beginning of the period of observation, no conclusions would be permissible. The clinical course in each rheumatic child cannot be predicted, but one can assume that children of the same age and with similar environmental surroundings might be reasonably expected to follow similar courses. Among the 75 treated children, 32 were free from rheumatic manifestations at the close of the period of observation; 16 of the control group were likewise free from their complaints. During the same period of time 38 of the treated group and 44 of the control group showed evidence of definite improvement. Five of the treated group and 15 of the con-

trol group remained unimproved. When the usual clinical tests of subjective and objective improvement are applied to each group, it becomes evident that those children who received regular daily doses of acetylsalicylic acid with magnesium oxide fared better than those not so treated.

Other observations were made on the 150 children in order to consider all of the factors which might have a bearing on the clinical course of the disease. The increase in height and weight was noted in each child, and this increase was compared in the two groups. The increment of growth and of changed weight was determined for the children observed. No change in the rate of gain in weight could be noted in the children who received acetylsalicylic acid with magnesium; actually the children not receiving it showed a slightly greater average gain. Individual children receiving the drug made gains in excess of the expected gain, but similar cases were noted among the controls. The doses of acetylsalicylic acid and magnesium oxide administered were small, and it is doubtful whether any nutritional improvement can be demonstrated where such small amounts are given.

TABLE I

AVERAGE INCREASE IN HEIGHT AND WEIGHT REGARDLESS OF COMPLAINT BUT ACCORDING TO AGE GROUPINGS

	TREATED GROUP		UNTREATED GROUP	
	WEIGHT IN POUNDS	HEIGHT IN INCHES	WEIGHT IN POUNDS	HEIGHT IN INCHES
Under 6 years	3.67	2.08	5.72	2.34
6 to 10 years	6.49	1.93	5.85	2.08
10 years and over	6.07	1.72	7.90	1.71
All ages (Total)	5.76	1.87	6.45	1.97

The presence or the absence of the tonsils in these rheumatic children has also been considered. It will be noted that somewhat more of the children in the treated group had their tonsils removed prior to the period of observation.

TABLE II

THE STATUS OF THE TONSILS IN RHEUMATIC CHILDREN UNDER OBSERVATION

	TREATED GROUP	UNTREATED GROUP
Tonsils still in	8 (10%)	16 (21%)
Tonsils out prior to study	53 (71%)	46 (62%)
Tonsils out during study	14 (19%)	13 (17%)

Previous studies by Kaiser[7] on the influence of the tonsils on the course of rheumatic infection showed no noticeable advantage in the escape of recurrences when the tonsils are removed after a rheumatic infection is once established. Inasmuch as the children considered

in this study had well-established evidence of a rheumatic infection and as the incidence of tonsil removal prior to the period of observation was much the same in both groups, it would seem that the presence or the absence of the tonsils would not need to be considered in evaluating the influence of the drug on the clinical course of rheumatic infections in children.

A rheumatic infection in a child is known to be a progressive one. An analysis was made of the observed children with reference to the duration of their rheumatic complaints. It was found that of the twenty-three treated children whose first attack of rheumatic infection occurred just prior to the period of observation, 56 per cent showed freedom from rheumatic trouble at the close of the period of observation; among the thirty-five control children whose first attacks were likewise immediately prior to this study, only 28 per cent showed freedom from rheumatic trouble at the end of the same period. Nine per cent of the treated children in this class showed no improvement, as compared with 23 per cent of the control group. When the history of rheumatic disease dated back for a number of years, no striking difference in the outcome of the treated and of the untreated children is noted. It appears that the prolonged treatment of a rheumatic child soon after the initial attack is desirable. No evidence is at hand to show whether these treated children who have shown improvement will be safeguarded against recurrent attacks over a period of years.

TABLE III

OUTCOME OF THE RHEUMATIC CHILDREN IN TERMS OF THE DURATION OF THE RHEUMATIC HISTORY

HISTORY	TREATED GROUP				UNTREATED GROUP			
	TOTAL	FREE	IMPROVED	UNIMPROVED	TOTAL	FREE	IMPROVED	UNIMPROVED
First attack	23	56%	35%	9%	35	28%	49%	23%
1-3 years' history	30	40%	57%	3%	26	12%	65%	23%
3-5 years' history	15	33%	60%	7%	6	33%	67%	–
5 or more years' history	7	29%	57%	14%	8	12.5%	75%	12.5%
Total	75	43%	50%	7%	75	21%	59%	20%

During the period of observation ranging from six to twelve months, there were four recurrences among the treated children and twelve among the controls. These recurrences were manifested by attacks of rheumatic fever or chorea, or by evidence of cardiac decompensation. With a recurrence incidence of 5 per cent in the children treated with acetylsalicylic acid and magnesium and of 16 per cent in the control children, it would seem that the drug administration was justifiable. However, a single year is not long enough to settle this

question. If such an advantage could be shown over a three- or a five-year period, it would seem advisable to treat the rheumatic child regularly over a long period of time.

COMMENT

The consideration of rheumatic disease as it manifests itself in children necessitates the recognition of numerous deviations from the normal state of well-being. Loss of appetite, pallor, chronic fatigue, fleeting pains, headache, nosebleed, nervousness, and other vague complaints can be noted in these children. These indefinite complaints usually are associated with the classical or major manifestations of rheumatic infection, but the more serious evidences of rheumatic disease may not be present. In considering the influence of any drug on these vague but real complaints, a suitable measuring stick is not available. Rest in bed may be as beneficial as the administration of a drug. Any mild infection, such as an upper respiratory disease, may bring a return of the mild rheumatic evidences. In this study an attempt was made to record the course of these mild and vague evidences. The course of the various states was so irregular that no dependable statistical estimate could be obtained. In general, the reports obtained from the parents of the treated children were more favorable than those received from the parents of the children who did not receive regular and prolonged drug treatment. A large percentage of the parents whose children received acetylsalicylic acid and magnesium wished to continue the administration of the drug to their children even after the period of study was concluded. These parents concurred in their belief that during the period of drug treatment the child's well-being was decidedly improved over previous years. The psychic effect of regular treatment may have something to do with this impression. However, added to the measurable benefits of regular drug treatment, the opinion of the parents may have some significance.

The control of rheumatic infection in children has not been effected. Certain specific procedures aid in its control, such as the removal of obvious foci of infection, e.g., infected tonsils and abscessed teeth, and relieving a sinus infection. Safeguarding a child against unnecessary upper respiratory infections aids in the control of rheumatic disease. Likewise removal to a tropical or subtropical climate is a procedure of definite value. For many children most of these procedures have been carried out, and the child is still subject to recurrent rheumatic attacks. Such a child is entitled to the regular and prolonged administration of some antirheumatic drug. The data gathered in this study would indicate that acetylsalicylic acid with the addition of magnesium oxide may benefit a certain number of these children. The beneficial effect will be noted chiefly in the subjective improvement of

the child, and probably fewer recurrences of a major rheumatic manifestation will occur. No untoward or unpleasant reactions were noted in any of the seventy-five children who received 10 or 15 grains of the drug daily for a period of from six to twelve months.

CONCLUSIONS

1. Two groups of rheumatic children of seventy-five each with similar manifestations were observed over a period of from six to twelve months.

2. The treated group received daily from 10 to 15 grains of acetylsalicylic acid with magnesium oxide.

3. The treated group showed a decided improvement over the untreated group in the children who had rheumatic pains alone.

4. The treated children with chorea likewise fared better than did the control group not so treated.

5. No measurable benefit could be noted in the treated group who showed evidence of rheumatic carditis alone.

6. The vague or milder manifestations of rheumatic infection were relieved in more of the treated children than in the control children.

7. There were fewer recurrent attacks of major rheumatic manifestations in the treated group than in the control group.

8. No untoward or unpleasant reactions were noted in any of the treated cases.

9. It would seem that acetylsalicylic acid with the addition of magnesium oxide is preferable to other antirheumatic drugs when used over a long period of time.

REFERENCES

1. Leech, Clifton B.: J. A. M. A. **95**: 932, 1930.
2. Podolsky, E., and Goldstein, N.: M. J. & Rec. **134**: 139, 1931.
3. Birkhaug, K. E.: J. Infect. Dis. **48**: 212, 1931.
4. Winter, J. E., and Barbour, H. G.: Proc. Soc. Exper. Biol. & Med. **25**: 587, 1928.
5. Winter, J. E., and Richey, C. H.: J. Pharmacol. & Exper. Therap. **42**: 179, 1931.
6. Simon, F. A.: J. Lab. & Clin. Med. **16**: 1064, 1931.
7. Kaiser, A. D.: J. A. M. A. **103**: 886, 1934.

16 North Goodman Street

CERTAIN PHYSICAL AND PHYSIOLOGIC ASPECTS OF ADOLESCENT DEVELOPMENT IN GIRLS

HELEN B. PRYOR, M.D.
SAN FRANCISCO, CALIF.

A CAREFUL analysis of the growth spurt at puberty helps answer the question, "How do girls grow up as regards physical maturity?"

The change from the straight, boyish figure of the preadolescent girl to the more rounded, mature figure of the postadolescent girl is accompanied by the appearance of the secondary sex characteristics and the stabilizing of certain physiologic processes.

The significance and order of appearance of these various phenomena of normal development is of interest to all who deal with children. Possible interrelationships among these physical changes found by the serial study of adolescents may throw light on irregularities in development and help in understanding the normal process.

T. Wingate Todd, at a recent conference, stated that the attainment of adolescence is a feature of maturity progress rather than a stage in physical growth.

The process of maturing physically for the average requires about three years for girls and extends from the ages of ten and one-half to thirteen and one-half years. Establishment of the menstrual cycle usually is taken as the sign of physical maturity. There were very wide individual variations in chronological age, but when our group was considered as a whole, certain criteria of physiologic age appear to be remarkably uniform at the time of the establishment of the menstrual cycle.

Terman[1] found among gifted children in California 48 per cent of the girls menstruated before the age of thirteen years, while only 25 per cent of unselected girls did. Terman's gifted children were distinctly above average in physical development as judged by height and weight.

The data presented here were collected during the last four years and consist of measurements, observations, and photographs of one hundred girls aged 9.5 to 14 years, seen at the Institute of Child Welfare of the University of California. This Institute sample is a normal grade selection, consisting of children who in 1932 were in the high fifth and low sixth grades of five Oakland elementary schools. This

From the Institute of Child Welfare, University of California.

group were given clinical physical examinations every six months, and in addition, anthropometric measurements were made in duplicate by two physicians.

Height was checked by two observers and measured to millimeters. The child stood against a vertical surface, the 6-inch board to which the scale was glued, and a right angle box was used for a head square. Weights were taken on balance scales at the same time of day each time, the children wearing only the uniform provided for the examination. All anthropometric measurements were made next the skin and followed the international anthropometric agreement on technic. Children came in as near their birthdays as possible.

Observations on the size or stage of development of the secondary sex characteristics were done by comparing with definite standards as follows:

Axillary hair was rated:

A—Fine down, 2 to 4 mm. in length.
B—Semiterminals 5 to 10 mm. in length.
C—Terminals 10 to 24 mm. in length, sparse.
D—Terminals 25 mm. and over, dense.

Pubic hair was rated:

A—Down 2 to 3 mm. in length, unpigmented.
B—Semiterminals 4 to 10 mm. in length, rapid growth of down, slightly pigmented.
C—Terminals not over 25 mm. in length, sparse, fully pigmented, wavy.
D—Terminals same as C, only full density.

Size of thyroid was rated 0 to 4:

1—meaning slight,
2—meaning moderate, and
3—meaning definite lateral enlargement of both lobes. Rating 4 was reserved for pathologic enlargement of the gland.

We used Stratz' classification of the stages of development of the breast as follows:

1—Stage of neutral childhood consists of nipple and areola.
2—Stage of breast bud, cone-shaped protrusion of papillary ring.
3—Breast buds are separated from their muscular substratum by rapidly growing adipose tissue. Areola protrudes while nipples remain embedded.
4—Completed development. Areola becomes part of general protrusion and button-shaped nipples alone still protrude.

Priesel and Wagner,[2] in Vienna, reported that the appearance of extragenital sexual characteristics in girls takes place in the following order: rounding of hips, development of mammae, pubic hair, and axillary hair. Our findings at the Institute of Child Welfare are confirmatory of theirs in this regard.

Body build appears to be a factor in the age of attainment of pubescence.

Table I shows the distribution of one hundred girls with regard to age at the appearance of the menses and according to body build as measured by the width-length index. Seventy-four girls were pubescent, and twenty-six were nonpubescent. Catamenia was established

at the average age of 12.5 years for the first seventy-four girls. The whole group was classified by means of the width-length index of body build[3] into:

(1) Slender-built (4 to 15 per cent narrower than average for age).
(2) Medium (3.9 per cent narrower to 3.9 per cent broader than average).
(3) Broad-built (4 to 15 per cent broader than average).

TABLE I

ONSET OF CATAMENIA
DISTRIBUTED BY AGE AND BODY BUILD

PERCENTAGE BROADER OR NARROWER THAN AVERAGE FOR AGE	AGE IN YEARS AT ONSET OF CATAMENIA									
	10.5 10.9	11.0 11.4	11.5 11.9	12.0 12.4	12.5 12.9	13.0 13.4	13.5 13.9	14.0 14.4	14.5 14.9	15.0 15.4
+13 to +15%	x									
+10 to +12%		x	x							
+ 7 to + 9%		x	xx		xxx		x			
+ 4 to + 6%		xx		xxxxx	xxx	0	x	xx	0	
						xxxxx				
+ 0 to + 3%		xx	xxxx	xx	xxxxxx	x000	00	x000		
							0			
0 to − 3%			xxx	xxx	xxx	xxx00	xxxxxxx	00	00	
− 4 to − 6%			x		xx0	x	xxxx0	0		
− 7 to − 9%					0		xx		00	
−10 to −12%						x	0	0		0
−13 to −15%										

One hundred girls: 74 pubescent, indicated by x; 26 nonpubescent, indicated by 0; entered at time of last examination.

The broad-built girls in this series menstruated earlier than the slender-built ones. From the distribution table it will be seen that only one of the slender-built girls menstruated before the age of 12.5 years, while thirteen of the broad-built ones did. Conversely, five slender-built girls had passed their fourteenth birthday without menstruating, while only one broad-built one had.

Table II shows the effect of body build upon pubescence for one hundred girls aged 10.5 to 15.5 years. Catamenia had been established in 90.3 per cent of the broad-built girls as contrasted with 55 per cent of the slender-built ones.

TABLE II

EFFECT OF BODY BUILD ON PUBESCENCE:
DISTRIBUTION OF ONE HUNDRED GIRLS AGED 10.5 TO 15.5 YEARS

	SLENDER BUILD (4-15% NARROW) NUMBER OF CASES 20	MEDIUM BUILD (FROM 3.9% NARROW TO 3.9% BROAD) NUMBER OF CASES 50	BROAD BUILD (4-15% BROAD) NUMBER OF CASES 30
Nonpubescent	9	15	2
Pubescent	11	35	28
Average age at onset of catamenia	13.2 yr.	12.6 yr.	12.4 yr.

The average ages for the appearance of menses according to body build were:

28 Broad-built girls at age of 12.4 yr.
35 Medium-built girls at age of 12.6 yr.
11 Slender-built girls at age of 13.2 yr.

Obviously the average age for the slender-built group will be pushed later than 13.2 years, since 45 per cent of them had not yet menstruated at age 12.6, which was average for the group as a whole. The average age of the twenty-six girls who had not menstruated was 13.9 years. Two of them were broader than average for their ages; nine were narrower than average; and fifteen were of average build.

It is interesting to use a stricter classification of body build and separate the extremely broad and extremely narrow girls into linear and lateral body types.[4] *Linear type* designates those 7 per cent or more narrower than average, while *lateral type* designates those 7 per cent or more broader than average for age in terms of width-length indices. It will be seen from the distribution table that there were nine "linear type" and ten "lateral type" girls in this series of 100 girls. Nine of the ten lateral type had menstruated before the age of 13 years, while none of the linear type had menstruated at the age of 13 years. At the time of the last examination when the girls were 13 and 14 years of age, six of the linear type had not yet menstruated, while all of the lateral type had.

Confirmatory evidence of a relationship between body build and pubescence very kindly was made available by Dr. C. P. Stone, of Stanford University, from physical data collected in the public schools. Height, weight, and width measurements were made as a part of his study of adolescents undertaken for the National Research Council.

Heights, weights, and width-length indices were arranged by age intervals of six months, from 11 to 14.5 years for pubescent and nonpubescent girls. Table III summarizes this data and shows that pubescent girls were broader at all ages than nonpubescent girls when classified by the width-length index and matched for age. The pubescent girls averaged from 13 to 25 pounds heavier, and from 1.2 to 3.6 inches taller than the nonpubescent girls at the various age levels.

In a second paper dealing with college women two conclusions of Barker and Stone[5] were: 1. "The girls who become pubescent relatively late continue to increase in weight during the college years slightly more rapidly than the early pubescent girls. 2. Correlational studies of menarcheal age in relation to indices of body build (bi-iliac/height) indicate that the women with late menarcheal ages tend toward the longitudinal (leptosomatic) type, whereas those with early menarcheal ages tend toward the lateral (pyknic) type."

Scheyer[6] studied the relation between body build and menarcheal age in 300 adult patients in a gynecologic clinic. He found that those

of stocky build (pyknic) are pubescent, on the average, significantly earlier than those of slender (leptosomatic) build. Gordon[7] made the same observation upon Smith College women. So far as they go, it will be seen their results confirm those of the present investigation.

TABLE III

HEIGHT, WEIGHT, AND RELATIVE WIDTH OF 192 PUBESCENT GIRLS COMPARED WITH 230 NONPUBESCENT GIRLS MATCHED FOR AGE*

AGE IN YEARS	PUBESCENT				NONPUBESCENT			
	NO. CASES	AVERAGE HEIGHT IN INCHES	AVERAGE WEIGHT IN POUNDS	AVERAGE WIDTH-LENGTH INDEX OF BODY BUILD	NO. CASES	AVERAGE HEIGHT IN INCHES	AVERAGE WEIGHT IN POUNDS	AVERAGE WIDTH-LENGTH INDEX OF BODY BUILD
11.0	5	60.3	104.1	162.4	19	56.7	82.7	157.6
11.5	11	61.3	104.2	163.1	21	58.1	86.3	158.2
12.0	24	61.9	106.5	162.8	38	59.4	92.8	159.1
12.5	52	62.4	113.4	163.9	52	60.3	95.8	159.3
13.0	38	62.9	113.8	164.1	38	61.2	97.9	158.7
13.5	25	63.6	117.4	165.5	25	61.4	99.8	159.5
14.0	22	63.7	123.0	164.7	22	62.0	95.4	158.7
14.5	15	64.6	125.6	164.6	15	63.0	99.4	162.8

The pubescent girls were taller, heavier, and broader at all ages than the nonpubescent girls.

*The raw data from which this table was calculated were made available to the author from an unpublished study in personality traits in adolescent girls financed by the Committee for Research on Problems of Sex, National Research Council. The funds and the study were administered by Prof. C. P. Stone, Stanford University.

Nobecourt[8] reported that the adolescent growth spurt in height extends from 9 to 15 years, with a very rapid increase from 9 to 12 and somewhat less rapid from 12 to 15 years of age in girls of average stature.

We have studied the height and weight increases at six-month intervals for three years beginning at age 10.5 years on eighty girls for whom we had complete records. A period of very rapid growth precedes the establishment of the menstrual cycle. The lengthening out process appears to come first and to be quite evenly distributed through the eighteen months before the cycle is established; although gains in both height and weight are much accelerated during the six months immediately before the first menstruation.

Table IV shows the growth in height for forty pubescent girls compared with forty nonpubescent girls matched for chronologic age, and extending over the same period of eighteen months. Column 1 shows the number of centimeters of height added during the six months immediately preceding catamenia, and Column 2, the number added during the twelve months before that.

The third and fourth columns show serial height gains for periods of six months and one year, respectively, for nonpubescent girls and represent the same calendar dates as the first two columns.

The pubescent girls made an average gain in height of 3.76 cm. (1.5 in.) during the six months before the appearance of menses, and

averaged 6.88 cm. (2.7 in.) for the one year period preceding that. This height gain shows only a moderate acceleration during the last six months before catamenia, since they were growing at the average rate of 3.44 cm. (1.4 in.) before that.

But when the pubescent group is compared with the nonpubescent group the accelerating effect of the oncoming catamenia is seen for

TABLE IV

ADOLESCENT GROWTH SPURT SHOWN BY GAIN IN HEIGHT

PUBESCENT		NONPUBESCENT	
COLUMN 1 FOR PERIOD OF 6 MO. JUST PRECEDING CATAMENIA (CM.)	COLUMN 2 FROM 18 MO. TO 6 MO. PRECEDING CATAMENIA (CM.)	COLUMN 3 FOR PERIOD OF 6 MO. CORRESPONDING TO COLUMN 1 IN DATES (CM.)	COLUMN 4 FOR PERIOD OF 1 YR. CORRESPONDING TO COLUMN 2 IN DATES (CM.)
3.4	9.6	2.0	6.7
3.2	9.2	2.4	4.6
4.0	6.0	1.9	4.3
3.6	5.8	2.8	5.0
4.7	8.9	3.5	7.5
1.5	5.2	3.6	7.0
5.0	5.0	2.5	4.5
3.7	4.0	2.3	3.3
3.4	7.1	2.4	5.9
2.9	3.8	3.1	4.8
4.2	9.0	3.2	8.0
3.4	8.0	2.4	4.8
3.4	7.7	2.4	6.0
5.7	3.5	3.0	6.8
4.6	8.0	4.1	7.9
3.5	6.0	2.6	11.4
4.5	4.2	4.6	8.1
4.7	9.3	4.6	5.8
3.3	4.9	1.9	8.3
2.3	7.5	1.9	5.8
4.0	7.3	3.9	7.0
4.0	7.4	2.0	4.8
2.5	7.2	2.2	5.9
3.7	6.4	2.7	6.0
1.4	6.6	2.6	8.8
6.2	5.5	3.6	6.1
3.7	7.3	2.1	7.2
4.6	4.2	3.5	8.7
3.4	8.8	2.8	5.0
4.4	8.4	2.3	4.5
2.8	8.8	3.7	5.2
4.3	6.8	3.5	8.7
3.8	7.9	3.2	6.0
2.9	7.6	3.3	8.7
3.7	8.0	1.2	2.6
4.4	3.6	4.1	7.9
3.4	8.6	4.4	7.7
2.2	7.8	4.3	7.2
4.3	9.0	3.2	4.8
6.2	5.5	4.0	6.2
Total 150.6	Total 275.4	Total 119.8	Total 255.5
Average 3.76	Average 6.88	Average 2.99	Average 6.39

the whole period of 18 months. The pubescent girls grew an average of 10.64 cm. (4.2 in.), while the nonpubescent grew an average of 9.38 cm. (3.7 in.). Furthermore, the pubescent girls grew 26 per cent faster than the nonpubescent during the last six months before appearance of menses.

TABLE V

ADOLESCENT GROWTH SPURT SHOWN BY GAIN IN WEIGHT

PUBESCENT		NONPUBESCENT	
COLUMN 1 FOR PERIOD OF 6 MO. JUST PRECEDING CATAMENIA	COLUMN 2 FROM 18 MO. TO 6 MO. PRECEDING CATAMENIA	COLUMN 3 FOR PERIOD OF 6 MO. CORRESPONDING TO COLUMN 1 IN DATES	COLUMN 4 FOR PERIOD OF 1 YR. CORRESPONDING TO COLUMN 2 IN DATES
5.7	6.1	2.3	5.0
2.1	4.4	3.4	6.4
2.6	6.3	2.6	3.1
4.0	5.0	2.5	8.8
4.2	6.4	2.7	5.8
9.7	4.8	3.9	4.7
2.8	3.8	1.3	1.2
3.0	8.2	1.1	5.0
2.7	4.4	2.7	5.8
2.1	7.2	2.4	7.0
4.3	5.9	2.7	4.1
4.9	9.9	0.5	4.4
4.4	7.0	1.0	3.3
8.7	6.5	2.9	6.9
4.3	7.3	2.5	2.0
1.5	0.0	1.9	4.5
5.4	8.1	4.4	4.6
5.0	8.2	1.0	3.9
3.8	3.0	4.7	8.6
4.1	7.5	2.7	4.5
4.6	4.3	2.3	2.5
2.6	4.2	3.9	4.7
1.7	5.3	2.3	4.2
5.1	11.4	1.9	3.3
2.5	4.7	0.7	1.7
2.4	4.3	3.4	2.5
2.1	2.0	0.2	2.6
5.9	5.7	0.8	4.0
3.1	5.4	1.7	2.2
1.8	1.9	1.0	4.7
4.2	3.4	1.1	5.3
7.2	6.1	3.3	3.4
5.8	3.1	1.0	3.8
3.6	5.8	2.2	5.6
3.8	3.6	3.0	4.9
8.2	1.1	3.5	6.8
5.6	5.6	5.6	4.0
5.0	3.3	8.8	10.5
3.0	6.8	0.5	4.6
4.6	4.1	2.4	4.1
Total 168.1	Total 212.1	Total 198.8	Total 185.0
Average 4.20	Average 5.3	Average 2.47	Average 4.62

Serial gains in weight measured in kilograms for forty pubescent and forty nonpubescent girls of similar ages for same periods of time.

A weight spurt parallels the height spurt and appears to be specifically stimulated by the approach of catamenia.

Beginning with eighteen months before the appearance of regular menstruation, weight gains recorded at six-month intervals will be seen in Table V for forty pubescent girls and forty nonpubescent girls.

The number of kilograms gained during the six months immediately preceding the first regular menstrual period, is shown in the first column. The second column of figures shows the number of kilograms gained by the same girls during the one-year period preceding the first column data, or from eighteen months to six months before catamenia.

The third and fourth columns show serial weight gains for periods of six months and one year, respectively, for nonpubescent girls and represent the same calendar dates as the first two columns.

The weight spurt that occurs during the six months just preceding appearance of catamenia caused forty girls to make an average gain of 4.2 kg. (9.2 pounds), or almost twice as much as forty other girls of the same ages who were nonpubescent and averaged 2.47 kg. (5.4 pounds) during the same period of time. The nonpubescent girls showed a fairly even rate of gain in weight for eighteen months—2.47 to 2.31 kg. (5.4 to 5.1 pounds) per half year, whereas the pubescent girls gained weight 59 per cent faster during the six months preceding catamenia than they averaged per half year for the previous year; 4.2 compared to 2.7 kg. (9.2 compared to 5.9 pounds).

Studies of nutrition in relation to relative width of the body[9] show that the broad-built have more subcutaneous tissue than the narrow-built and tend to put on weight much more easily at all ages.

Davenport[10] has stated that development of weight in man is the resultant of many more or less elementary growth processes and that the adolescent spurt may be activated by the secretions of the pituitary gland, since adolescent hypophyseal underactivity results in reduced growth while preadolescent hyperactivity results in giant growth.

One of the conclusions of Paul Godin's[11] interesting study of growth during school age is that puberty is purely a germinal affair, and the maturity of the germ itself, an affair of nutrition. With Godin's conclusion in mind, possibly the glandular balance of the broad-built child tends to help him (or her) arrive at the optimum state of nutrition for pubescence sooner than the narrow-built child who is so frequently underweight.

Tables VI and VII show the stage of development of pubic and axillary hair for all of the examinations. At the onset of catamenia, regardless of chronologic age, the prevailing hair pattern was for axillary, stage B, and for pubic, stage C. At the onset of menses the cases were distributed as seen in Table VIII.

TABLE VI

STAGE OF DEVELOPMENT OF AXILLARY HAIR: TABLE OF DISTRIBUTION BY AGE

STAGE OF DEVELOPMENT	AGE IN YEARS											TOTALS
	10.0 10.4	10.5 10.9	11.0 11.4	11.5 11.9	12.0 12.4	12.5 12.9	13.0 13.4	13.5 13.9	14.0 14.4	14.5 14.9	15.0 15.4	
0	17	36	44	40	28	17	5					187
A	1	12	19	20	20	19	13	9	1		1	115
B		5	11	17	15	23	17	12	7			107
C		1	4	10	23	20	29	28	16	6		137
D				4	4	14	21	24	13	11	2	93
Totals	18	54	78	91	90	93	85	73	37	17	3	639

TABLE VII

STAGE OF DEVELOPMENT OF PUBIC HAIR: TABLE OF DISTRIBUTION BY AGE

STAGE OF DEVELOPMENT	AGE IN YEARS											TOTALS
	10.0 10.4	10.5 10.9	11.0 11.4	11.5 11.9	12.0 12.4	12.5 12.9	13.0 13.4	13.5 13.9	14.0 14.4	14.5 14.9	15.0 15.4	
0	9	13	7	6	2	1						38
A	8	25	40	29	20	8	4	1				135
B	1	10	17	26	26	21	8	3	1	1		114
C		6	10	22	25	43	29	15	5	1	1	157
D			4	8	17	15	34	29	16	7		130
E						5	10	25	15	8	2	65
Totals	18	54	78	91	90	93	85	73	37	17	3	639

TABLE VIII

AXILLARY AND PUBIC HAIR AT ONSET OF CATAMENIA

AXILLARY HAIR AT ONSET OF MENSES		PUBIC HAIR AT ONSET OF MENSES	
DEVELOPMENT STAGE	NUMBER OF CASES	DEVELOPMENT STAGE	NUMBER OF CASES
A	9	A	0
B	41	B	4
C	18	C	48
D	6	D	22
	74		74

Table IX shows the various stages of development of the breast for all of the examinations. At the onset of catamenia regardless of chronologic age, the breast development summarized in Table X will be seen to be quite uniform.

Table XI illustrates the distribution of so-called adolescent goiter. All but one of the seventy-four girls in this series who were pubescent showed enlargement of the thyroid gland at the time of the establishment of the menstrual cycle. At the onset of catamenia the cases were distributed as seen in Table XII.

These overwhelmingly predominant patterns of axillary and pubic hair, development of breast, and enlargement of thyroid as described,

demarcate a physiologic age which is much more constant than the chronologic age at the onset of catamenia.

TABLE IX

STAGE OF DEVELOPMENT
BREAST DEVELOPMENT
DISTRIBUTION TABLE BY AGE

STAGE OF DEVELOPMENT	AGE IN YEARS											TOTALS
	10.0 10.4	10.5 10.9	11.0 11.4	11.5 11.9	12.0 12.4	12.5 12.9	13.0 13.4	13.5 13.9	14.0 14.4	14.5 14.9	15.0 15.4	
0	17	32	24	14	10	8	2	1				108
1	1	17	32	32	26	16	5	3				132
2		2	14	27	30	21	22	9	5	1		131
3		2	7	16	17	34	30	22	13	3	2	146
4		1	1	2	7	14	21	34	17	6	1	104
5							5	4	2	7		18
Totals	18	54	78	91	90	93	85	73	37	17	3	639

TABLE X

BREAST DEVELOPMENT AT ONSET OF MENSES

DEVELOPMENT STAGE	NUMBER OF CASES
0	0
1	1
2	28
3	33
4	12
	74

TABLE XI

STAGE OF DEVELOPMENT
THYROID
DISTRIBUTION TABLE BY AGE

STAGE OF DEVELOPMENT	AGE IN YEARS											TOTALS
	10.0 10.4	10.5 10.9	11.0 11.4	11.5 11.9	12.0 12.4	12.5 12.9	13.0 13.4	13.5 13.9	14.0 14.4	14.5 14.9	15.0 15.4	
0	5	5	10	8	7	1	2	3	3	2		46
1	8	22	29	31	23	23	30	25	12	4		207
2	4	23	30	39	45	54	32	31	14	6	2	280
3	1	4	8	13	15	15	21	14	8	4	1	104
4			1							1		2
Totals	18	54	78	91	90	93	85	73	37	17	3	639

TABLE XII

SIZE OF THYROID AT ONSET OF MENSES

DEGREE OF ENLARGEMENT	NUMBER OF CASES
0 None	1
1 Slight	16
2 Moderate	47
3 Definite	10
4 Pathologic	0
	74

CONCLUSIONS

A serial study of the adolescent growth spurt was made on one hundred girls. Examinations extending over four years, at half-year intervals, demonstrated a period of very rapid growth during the six-month period immediately preceding the onset of catamenia.

Gain in height preceded gain in weight and was quite evenly distributed over a period of eighteen months.

Pubescent girls averaged a height increase of 10.64 cm. in eighteen months, compared to 9.38 cm. for nonpubescent girls.

The rate of height gain for pubescent girls during the last six months before the appearance of menses was 26 per cent faster than for nonpubescent girls during the same period of time.

Gain in weight was specifically stimulated by approaching menses. Pubescent girls gained weight 55 per cent faster during the six months just preceding catamenia than they did during the one year before that.

Pubescent girls gained twice as much weight during the last six months before the appearance of menses as nonpubescent girls did during the same calendar months.

Girls of broad body build in this series menstruated earlier than girls of slender body build.

Pubescent girls were consistently taller, heavier, and broader than nonpubescent girls of similar ages in a series of 422 cases.

A predominant pattern of development of pubic and axillary hair accompanied the onset of catamenia regardless of chronologic age. A certain degree of enlargement of the thyroid gland appeared destined to accompany the first appearance of menses. A fairly constant stage of development of the breast was seen regularly at the same time.

Interrelationships among certain secondary sex characteristics suggest themselves as criteria of a physiologic age which is much more constant than chronologic age for predicting the onset of catamenia.

REFERENCES

1. Terman, Lewis M., and others: Mental and Physical Traits of a Thousand Gifted Children: Genetic Studies of Genius, Vol. 1, Stanford University, 1925, Stanford University Press.
2. Priesel, R., and Wagner, R.: Ztschr. f. Konstitutionslehre 15: 333, 1931.
3. Pryor, Helen B., and Stolz, Herbert R.: J. PEDIAT. 3: 608, 1933.
4. Lucas, W. P., and Pryor, Helen B.: J. A. M. A. 97: 1127, 1931.
5. Barker, R. G., and Stone, C. P.: Physical Development in Relation to Menarcheal Age in University Women. Ms.
6. Scheyer, H. E.: Ztschr. f. Geburts. u. Gynäk. 102: 579, 1932.
7. Gordon, F. F.: Am. J. Pub. Health 20: 963, 1930.
8. Nobecourt: Rev. gén. de clin. et de thérap. 44: 561, 1930.
9. Franzen, R.: Physical Measures of Growth and Nutrition, American Child Health Association, 1929.
10. Davenport, C. B.: Body Build and Its Inheritance, Carnegie Institute, Washington, D. C., 1923.
11. Godin, Paul: Growth During School Age, Boston, 1927, Gorman Press.

FIBROMA OF THE MESENTERY

Report of a Case in a Six-Day-Old Infant

Ogden C. Bruton, M.D.
Nashville, Tenn.

THE following case is reported because reference to the literature establishes it as a medical rarity.

J. M., a six-day-old white male infant, was admitted on the pediatric service of the Vanderbilt University Hospital Dec. 6, 1934. He was the last child of seven normal pregnancies and weighed 10 pounds at birth. Shortly after birth he was given water and put to the breast, but soon vomited and continued to do so until his admission. The vomitus always contained bile, was never noted to contain fresh blood, and in the twenty-four hours previous to admission was not unlike the stools. Since birth he had had five stools, all of which were small and consisted of meconium, save the last one which was quite large, loose, and was thought to contain a small amount of digested food. No blood was recognized in the stools. He had grown progressively more drowsy, cried very little, nursed less well, voided infrequently, and developed a slight icteric tint to the skin.

He was a dehydrated, slightly icteric newborn who slept peacefully. Other important positive findings were confined to the abdomen. It was slightly distended and patterns of distended loops of intestine were visible and were seen to change slowly as peristalsis set in. The peristalsis was most marked in the left upper quadrant and moved from right to left. The overlying skin was loose, and the abdominal musculature very relaxed, making palpation of the viscera easy. In the lower abdomen a firm, multinodular, kidney-shaped mass, measuring about 5 by 3 by 3 cm., could be pushed about at will. The mass was apparently not attached to the anterior abdominal wall. There were no other masses or enlarged viscera. The testicles were palpable in the scrotum.

It was obvious that the infant suffered from an intestinal obstruction, and it was thought that the obstructing agent was a neoplasm. Laboratory findings were essentially normal, and the clotting time was five minutes.

Ten hours after admission the patient was transferred to the surgical service for abdominal exploration. After the peritoneum was opened, tremendously distended and collapsed loops of intestine were visible. Both collapsed and distended bowel ended in a large nodular tumor, which lay in the mesenteric border of the intestine, approximately 15 inches below Treitz ligament. A portion of the jejunum 2 or 3 inches proximal and distal to the tumor, and including the tumor, was removed. A side to side anastomosis of small and distended gut was performed. The patient was returned to the ward in good condition but during the next thirty hours bled freely and continuously from the wound. This bleeding ceased immediately after the baby was transfused with blood. Feeding was resumed, and three days after the operation the baby passed two normal stools. Vomiting continued in lessened amounts for four days. The remainder of his two-week stay in the hospital was uneventful.

The tumor consisted of a clam-shaped specimen measuring 5 by 4.5 by 2 cm., made up of a U-shaped loop of small intestine with intervening mesentery containing a

From the Department of Pediatrics, Vanderbilt University Hospital.

large multinodular white tumor mass (Fig. 1). The proximal portion of the intestine was markedly dilated while the portion distal to the tumor mass was so small that a probe filled the lumen. The intestine was opened, and at the junction of these two types of intestine, as described, a moderately firm tumor mass filled the

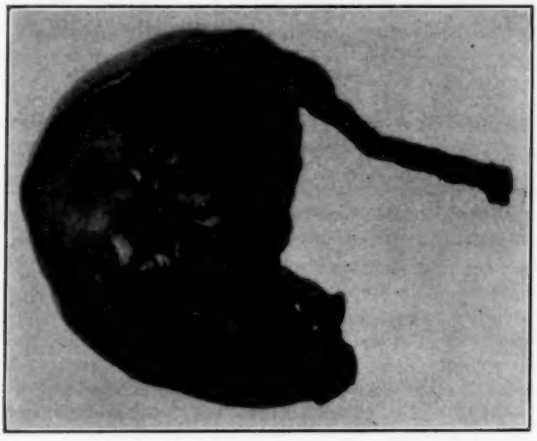

Fig. 1.—Gross appearance of tumor mass.

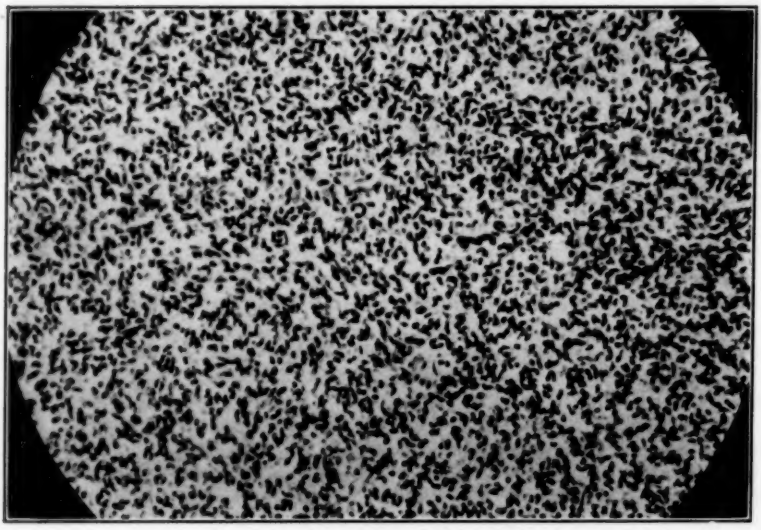

Fig. 2.—Microscopic section (low power).

lumen. By carefully inserting a probe the tumor was divided. It had extended from each side and formed a flattened passageway through which food could have passed only with great difficulty.

All sections showed a homogeneous sharply circumscribed tissue composed entirely of connective tissue cells with large nuclei and indistinct cytoplasm (Fig. 2). At the

periphery the cells were flattened and merged into a thick fibrous capsule. No mitotic figures were present. The tumor was diagnosed as a fibroma by Dr. Brooks and Dr. Goodpasture of the surgical and pathological departments.

At six months of age the patient is apparently a normal, healthy baby weighing 15 pounds.

To date we have been able to find only three reports of similar tumors occurring in children. Greer[1] in 1911, in a report that summarized thirty-three cases of mesenteric tumors, included one fibroma in a girl ten years old. Summers,[2] in 1932, briefly reviewed the literature and contributed a case of a similar tumor found in a three-year-old girl. Weaver,[3] in 1933, added a third case to the list in a ten-year-old colored female. Seemingly our case is the fourth to be reported in a child and is unique in that it occurred in a newborn infant.

REFERENCES

1. Greer, W. J.: Brit. M. J. 2: 1085, 1911.
2. Summers, J. E.: Surg. Gynec. Obst. 55: 244, 1932.
3. Weaver, Olin H.: J. M. A. Georgia 22: 295, 1933.

CHILDHOOD LEUCEMIA

MILA PIERCE, M.D.
CHICAGO, ILL.

WHEN leucemia runs a typical course in children, it is not difficult to recognize. But familiar both to the pediatrician and pathologist are the problems involved in differentiating acute leucemia from sepsis. A survey of the cases of leucemia seen at the Children's Memorial Hospital during the past twenty years emphasizes the frequency with which this problem is met and may, therefore, be of interest to the clinician.

This review of forty-one cases, sixteen of which came to autopsy, is simplified by arranging them in three groups according to the trend of the leucocyte curve throughout the course of the disease since such grouping defines three clinical types, each presenting certain identifying features and diagnostic problems.

In Group I the leucocyte curve showed a sustained and marked elevation throughout the course of the disease, and immaturé leucocytic elements were constantly present.

In Group II the leucocyte curve showed a slight elevation, or even a depression to a leucopenic level, and immature leucocytes were absent, or inconstantly present.

In Group III the leucocyte curve showed a marked fluctuation from a hyperleucocytosis to a leucopenia, and the percentage of immature leucocytes was variable.

Group I represents those cases the clinical picture of which conformed to the classical textbook description of the disease, and is comprised of sixteen of the forty-one cases. The story was commonly that of a gradual onset of weakness, pallor, and fever in a previously well child. A period of vague absence of well-being, lasting from five to six weeks, terminated in a rapid development of extreme pallor, prostration, and hemorrhagic manifestations for which the parents sought the advice of the physician. The terminal period of acute illness was rarely longer than seven to ten days. The average duration of illness, from the onset of the first symptom to death, was seven weeks, the average duration of illness prior to admission 6.6 weeks and the average period of observation 3.1 days. It was made up of the youngest children in the series; the average age was 3.1 years, the youngest being 3 months and the oldest 10 years old. Of the seven children under one year of age, among the forty-one cases, six were in this group.

From The Children's Memorial Hospital.

Although the previous history was commonly negative, the history of an infection, dating to a time prior to the onset of leucemic symptoms, from which the child failed to recover normally, was obtained in five of the sixteen cases, or 30 per cent. In four of these children this antecedent illness was in the nature of a severe upper respiratory infection, and the fifth had had diphtheria five months earlier.

Some of the essential physical findings are mentioned as a matter of interest, although a detailed discussion will not be attempted, as little can be added to other reports in the literature.[1-6] During the prodromal stage the familiar triad of weakness, fever of a septic type, and pallor were the only constant findings. The first sign pointing to a primary disturbance of the hemopoietic system was the occurrence of purpuric areas in the skin and mucous surfaces. It was at this stage that the first blood examination was made in many of the cases. Ecchymoses were present at the time of admission in all cases and persisted throughout the course; these were uniformly accompanied by a thrombopenia and a prolonged bleeding time. Mucous membrane hemorrhages occurred in 50 per cent of these cases, and necrotic throat lesions, in 31 per cent. An absolute relationship between the degree of thrombopenia and mucous membrane hemorrhages could not be determined; several with platelet counts of less than 10,000 had no mucous membrane hemorrhages. Similarly no definite relationship was apparent between the total number of mature neutrophiles and the occurrence of necrotic throat lesions.

The superficial lymph nodes were enlarged in all cases although there was considerable variation in size in different individuals. Splenomegaly was encountered in twelve of the sixteen cases; in two the spleen was palpable, and in two it could not be felt. The degree of splenic enlargement did not constantly reflect the degree of leucocytosis: in the two cases in which the spleen was not palpable, the leucocyte counts were 71,000 and 193,000, respectively; in one in which it reached the crest of the ilium, the count was 20,000.

The first blood examination was sufficiently characteristic to establish the diagnosis of leucemia in the large majority of these cases, so constant were the findings of a marked leucocytosis, a high percentage of immature leucocytic elements, severe anemia, and thrombopenia. The total count was above 40,000 in all of these cases, and in nine it was well over 100,000 with only a narrow range of fluctuation in the total count throughout the period of observation. The immature leucocytes were lymphoblasts in eleven cases and immature myeloid elements in five cases.

In eight of these cases the clinical diagnosis was confirmed by necropsy findings. A review of the characteristic pathologic findings will be discussed later since there was no essential difference in the pathology of the three groups.

Two histories from Group I are given: Case 27, as a typical case which presented no special problems, and Case 41, as illustrative of certain atypical features. In the latter case an apparent relationship existed between the antecedent upper respiratory infection and the onset of the leucemic symptoms. The profound anemia, the leucocytosis with a high percentage of granulocytes but with only 8 per cent myelocytes, and the moderate degree of enlargement of the superficial lymph nodes and spleen made the clinical diagnosis of a leucemoid response to an infection a plausible one. The postmortem diagnosis of a myeloid leucemia was not made without reservation. The outstanding finding—namely, that of marked hyperplastic changes affecting the leucocytic and reticulum elements of the bone marrow, lymph nodes, and spleen, together with degenerative changes in the same organs—was of a degree sufficient to throw the weight of evidence in favor of a leucemic process. The absence of cellular infiltrations in other organs and of extra medullary myelopoiesis and the presence of a positive blood culture for *Streptococcus viridans* are points in favor of profound hyperplastic response to an infection.

CASE 27.—B. R., a five-month-old white female baby, was admitted May 11, 1931, with a history of having been normal in all respects until the age of three months, when she developed a fever and diarrhea. Pallor and blue spots in the skin were noted at this time. The diarrhea subsided after a few days, but she continued to grow more pale and irritable and often perspired freely. More ecchymoses were noted in the skin two days prior to admission. Twenty hours after admission she expired with a diagnosis of acute lymphatic leucemia.

Physical examination revealed a well-nourished and well-developed girl of five months of age whose temperature was 99° F. and whose respirations were rapid and pulse thready. The skin was markedly pale, and purpuric areas were present on the abdomen, neck, and arms; the mucous membranes of the mouth and throat were very pale; no petechiae were present. All of the superficial lymph nodes were enlarged; the spleen and liver were palpable three fingerbreadths below the costal margins. The heart was not enlarged, and no murmur was present. The lungs were negative. The blood findings were: erythrocytes, 1,440,000; hemoglobin, 18 per cent; leucocytes, 184,000 with 88 per cent medium-sized lymphocytes, 2 per cent neutrophiles, and 10 per cent large mononuclears. The platelets were decidedly reduced in number as estimated by the differential smear.

The necropsy findings were typical of acute lymphatic leucemia with generalized petechial hemorrhages of the skin, mucous membranes, and serous surfaces, with marked pallor of the organs, bilateral bronchopneumonia, perisplenitis, edema of the leptomeninges and craniotabes. Culture of the heart's blood on dextrose brain broth showed no growth.

Histologic sections showed an extensive infiltration of the organs with small and medium-sized lymphocytes. The spleen showed a loss of normal markings and a diffuse hyperplasia of lymphoid elements. The malpighian corpuscles were actively proliferative but did not stand out from the adjacent structures because of the general hyperplasia. The center of the germinal follicles, in which there were large vesicular reticulum cells and lymphocytes, was surrounded by a dense zone of small and medium-sized lymphocytes among which were many mitotic figures. The zone

merged into less crowded cellular pulp in which the same lymphoid cells predominated. Reticulum cells or phagocytes were not prominent. No areas of erythropoiesis were found. In the lymph nodes the same diffuse hyperplasia of lymphoid cells was evident. The markings were lost, and the germinal follicles could not be distinguished from the rest of the cellular pulp. Mitotic figures were present in large numbers, two to four to each oil immersion field. The predominating cell was the medium-sized lymphocyte whose oval nucleus was indented on one side by two or three deep folds of the nuclear membrane, giving it a somewhat wrinkled appearance on that side. The chromatin particles were fairly widely separated by nuclear sap; from one to two nuclei were present.

CASE 41.—L. H., an eleven-month-old white female baby, was admitted Nov. 25, 1934, with a history of having been well until two weeks previously when she had developed a "cold" with cough, fever of 102° F., and many canker sores in the mouth. Four or five days after the onset, swelling of the cervical lymph nodes was noted, and a few days later a macular eruption appeared on the chest and abdomen, the lesions being approximately 0.5 to 1 mm. in diameter. Following the eruption she seemed somewhat improved until two days before admission, when the mother noticed a "blue spot" on the left leg. More ecchymoses developed on the extremities and face in the next twenty-four hours, and the child appeared progressively more acutely ill and appeared to be in pain. No vomiting or bleeding from mucous surfaces had occurred. The child died three hours after admission.

Physical examination revealed an extremely pale though well-nourished and well-developed baby who was moribund. The skin had a waxy appearance, and ecchymoses of various sizes were present on the extremities, neck, and head, with fresh and fading petechiae over the entire surface of the body. The mucous membranes of the mouth and throat were pale. No petechiae were present, nor was there any bleeding of the gums. The cervical, axillary, and inguinal lymph nodes were palpable, though not greatly enlarged. The liver extended two fingerbreadths, and the spleen one fingerbreadth below the costal margin. Except for a few coarse bronchial râles in the lungs, the chest and heart were negative. No abnormal reflexes were present. The blood findings were: erythrocytes, 1.33 million; leucocytes, 80,000; hemoglobin, 30 per cent (Sahli); and the differential count: myelocytes, 8; juvenile neutrophiles, 8; stab neutrophiles, 21.5; segmented neutrophiles, 25.5; small lymphocytes, 31; medium-sized lymphocytes, 1.5; large lymphocytes, 2.5; large monocytes, 2; with 6 normoblasts per 200 leucocytes. The platelets were large and markedly reduced in number; the indirect count was 26,600. The clinical diagnosis was acute myelogenous leucemia, although a severe sepsis was considered.

The necropsy findings were, briefly: anatomic diagnosis myelogenous leucemia; myeloid infiltration and hyperplasia of the bone marrow and lymph nodes; large and small hemorrhages into the skin, subpleural space, kidneys, and epidural space; *Streptococcus viridans* septicemia.

Histologic study of the lymph nodes showed a marked hyperplasia of the reticulum and cellular stroma although the normal architecture was fairly well preserved. The follicles showed active proliferative changes, with a central zone made up of large vesicular lymphocyte, some nuclear débris, and a peripheral zone of closely packed small lymphocytes. The spleen showed a striking increase in the reticulum elements and also markedly active germinal centers similar to those of the lymph nodes. Among the large reticulum cells of the stroma was a liberal sprinkling of erythrocytes, and many large phagocytes containing nuclear débris—no areas of erythropoiesis were present.

The bone marrow of the rib and vertebra studied showed marked hyperplastic changes. The closely packed cellular stroma consisted of areas of dense accumulations of lymphoid cells or myeloblasts, and a few neutrophilic and eosinophilic myelocytes separated by less crowded zones where myelocytes, metamyelocytes, normoblasts, and megacaryocytes were more easily identified. Very few polymorphonuclear neutrophiles were present. The predominating lymphoid cells were classified as myeloblasts chiefly because of the presence of transition forms of granulocytes in the islands of immature cells.

Sections of the liver, kidney, lung, and heart did not show any cellular infiltrations typical of leucemia.

In Group II, consisting of thirteen cases, the clinical picture was less clearly defined, and the differentiation from a leucemoid response to an infection or from thrombopenic purpura was often difficult since the blood findings were less characteristic. The leucocyte curve was that of a moderate leucocytosis or even a leucopenia throughout the period of observation.

The clinical story was that of a less rapidly fatal course, the average duration of illness from onset to death being 10 weeks. A period of illness averaging 8.4 weeks occurred prior to the period of hospital observation, which averaged 8.1 days. It was a slightly older age group, the average age being 3.5 years. A history of an antecedent infection without normal recovery was obtained in seven of the thirteen cases, or 53 per cent; in two instances these were in the nature of upper respiratory infections; in one, a pyelitis; in two, pneumonia followed by abscess formation; and in two, fever of undetermined origin.

The history was commonly that of a prolonged period of vague illness, with progressive weakness, slight fever, and pallor, which culminated in a rather rapid onset of prostration, due probably to a severe anemia.

The constant physical findings, as in Group I, were those of generalized lymph node enlargement and ecchymoses. Hemorrhage from the mucous surfaces occurred in 69 per cent. The spleen was enlarged in all cases although it varied considerably and did not reflect the degree of leucocytosis in the peripheral blood. Necrotic throat lesions occurred in 23 per cent, as opposed to 21 per cent in Group I. This is interesting since the total neutrophile count was constantly lower than in Group I, and it might have been expected that necrotic lesions would have been seen more frequently. It appears, however, that this incidence of necrosis of mucous membranes is not dependent upon the neutropenic state alone since in several cases in which the total neutrophile count was less than 200, no such lesions occurred, and in others large necrotic areas developed with a total mature neutrophile count of over 2,000.

In ten of the thirteen cases, the leucocyte count ranged between 9,000 and 38,000. Three cases were seen only during a terminal leucopenic phase. Only three of the cases came to autopsy; in two the findings were typical of leucemia; in the third the possibility of sepsis could not be eliminated by the necropsy findings.

Two case histories are cited: Case 34, as typical of patients seen only during the aleucemic phase, and Case 32, as one in which the course suggested a thrombocytopenic purpura.

CASE 34.—A. L., a two-year-old girl of German extraction, was admitted to the hospital on Nov. 16, 1933, and expired four days later. The illness dated from one month prior to admission, when a swelling about the eyes and pallor were noted. Lassitude and anorexia became marked although the parents had not noted a fever. About two weeks later black and blue marks appeared on the limbs, and the cervical lymph nodes enlarged. The child had been well except for pneumonia in March, 1933, from which she seemed to have recovered satisfactorily and to have been well until July, when she developed a fever of 106° F. and was ill for several days. Following a short febrile period, two abscesses developed, one on the elbow and one in the right axilla. These, when lanced, drained a large amount of pus. The family history was negative except for contact with a tuberculous maternal aunt when the child was a year old.

The essential physical findings on examination were those of an acutely ill, well-developed, although poorly nourished, girl aged two years and ten months, who was strikingly pale, with a slightly greenish color. Numerous petechiae and purpuric areas were scattered on the extremities and trunk. The tongue showed hemorrhagic areas near the tip, the pharynx was ulcerated, and the uvula was crusted with a grayish exudate. Petechial hemorrhages were present on the palate and tonsils. There was a purulent nasal discharge. The cervical lymph nodes were the size of a large walnut, soft and boggy but not fluctuant; the inguinal and axillary nodes were bean-sized. The heart and lungs were negative. The liver was palpated three fingerbreadths below the right costal margin, and the spleen, one fingerbreadth below the left costal margin. The blood findings on admission were: erythrocytes, 1,500,000; hemoglobin, 21 per cent; platelets, less than 10,000; leucocytes, 5,500, with 5 per cent juvenile forms and 4 per cent stab forms; lymphocytes, small, 77, medium, 7; lymphoblasts, 3; monocytes, 4; basophilic erythroblasts, 7. (See Table I for further counts.)

TABLE I

BLOOD FINDINGS (CASE 34)

DATE	HB.	R.B.C.	PLATELET	W.B.C.	POLYMORPHS	LYMPHOCYTES	MONOCYTES	EOSINOPHILES	BASOPHILIC ERYTHROBLASTS
11/16/33	21	1.50	10,000	5,500	9	87	4	1	7
11/17/33	33	1.10		3,300	5	93	2		6
11/18/33	31	0.85		2,300					
11/19/33	25	0.51	12,500	1,000	2	97	1		0
11/20/33				850	0	100	0		0

During the three days of observation the patient ran a febrile course with a temperature around 105° F. and became progressively weaker until death. The red count fell rapidly to 500,000 and the leucocytes to 850. The patient was given a

nucleotide therapy of pentnucleotide K 96 in doses of 5 c.c. intramuscularly twice daily with no increase in the neutrophiles or the total leucocyte count. Juvenile and stab forms among the neutrophiles and a few basophilic erythroblasts decreased in number as the percentage of lymphocytes increased. It is noteworthy that typical lymphoblasts were not found after the first blood examination; however, most of the lymphocytes were young forms—with a basophilic cytoplasm at all times. The clinical diagnosis of aleucemic leucemia was made on the basis of the marked generalized lymphadenopathy; the widespread petechiae and tendency to hemorrhage; the marked ulceration of the throat; and the presence of lymphoblasts in the early smears, together with the reduction in platelets and severe anemia. Sepsis with leucopenia was considered because of the rapid drop in the total leucocyte count and the reduction in granulocytes and was not ruled out with certainty except by necropsy findings. It was on the assumption that such was the diagnosis that nucleotide therapy was given.

The anatomic diagnosis postmortem was: lymphatic leucemia; lymphoid infiltrations of lymph nodes, liver, spleen, kidneys, and bone marrow; generalized pallor; hemorrhages into the skin, pleura, epicardium, renal pelvis, and mucosa of esophagus and stomach; arteriosclerosis of aorta; focal necrosis in the bone marrow; streptococcus septicemia; right pleural adhesions. Briefly, histologic sections showed a moderate degree of infiltration of the organs with lymphoid cells. In the liver there were moderately large infiltrations about each periportal space, with lymphoid cells with irregular nuclear outlines, and smaller accumulations in the central portions of the lobules and capillary spaces. In the kidney the infiltration was less marked and limited to the intermediary zone between the cortex and medulla. The glomeruli were unchanged. The malpighian bodies of the spleen were large and prominent and showed a marked hyperplasia of the germinal centers; the architecture of the lymph nodes was somewhat obscured by active hyperplasia of the cellular elements, and the germinal centers were markedly hyperplastic with immature lymphoid cells. The vertebral bone marrow was grossly dull red with areas of brownish gray interspersed throughout its substance. In the sections it was seen to consist largely of small lymphoid cells with a heavy irregular cell outline and a narrow rim of cytoplasm. There were areas of erythropoiesis but very few myelocytes and no mature polymorphonuclear cells to be seen.

Case 32.—A. M., a two-year-old boy of Polish parentage, was admitted on Sept. 20, 1933, and expired thirty hours later. He had been well until six weeks previously, when he complained of abdominal pain and was seen by a physician who diagnosed it "heart trouble." The abdominal pain continued intermittently until two weeks prior to admission, when it was noted that he was becoming progressively weaker and more pale and was running a fever. During the two days before admission he had had several mild nosebleeds, and black and blue spots were noted in the skin.

The essential findings on admission were those of a well-nourished, very pale, but not acutely ill child who was moderately dyspneic. The skin was moist and had a yellowish pallor, and there were petechiae and small ecchymotic areas on the trunk and extremities. The ocular fundi showed small retinal hemorrhages, and crusts of old blood were present in the nares. Petechiae were present on the palate and tonsils. The throat was not necrotic, nor was there any gross bleeding from the throat or gums. The superficial lymph nodes were small bean-sized in the cervical, axillary, and inguinal regions. The spleen was enlarged to 8 cm. below the left costal margin. The chest was negative except for a hemic heart murmur. The blood count was: red blood cells, 1,650,000; hemoglobin, 15 per cent (Sahli); leucocytes, 38,850; platelets, 15,000, with a differential count of 91 per cent lymphocytes, 5 per cent neutrophiles, 2 per cent monocytes, and 2 per cent eosinophiles. The bleed-

ing time was prolonged to thirty minutes; the coagulation time was six minutes. The following day the leucocyte count was 11,500, and the differential count as follows: neutrophiles, segmented, 11; stab, 3; lymphocytes, medium-sized, 82; blasts, 3. The spleen had reduced slightly in size. Roentgen ray examination of the chest showed no evidence of mediastinal gland enlargement, nor was there evidence of leucemic bone changes. On the following day, after a transfusion, the child expired. The diagnosis of acute lymphatic leucemia was made with some reservation in this case, the lack of toxicity, the moderate enlargement of the spleen, the low percentage of lymphoblasts, and the low-grade fever suggesting the possibility of a thrombocytopenic purpura.

The necropsy findings of Dr. Allan Roos were: lymphatic leucemia; lymphoid infiltration in myocardium, liver, spleen, and bone marrow; generalized enlargement of the lymph nodes and lymphatic structures of intestines; hemorrhages into skin, serous surfaces, epicardium, myocardium and endocardium, pleura and lung, peritoneum, stomach, jejunum and intestinal lumen, bladder wall, hepatic and renal capsules; fresh aspiration pneumonia; Meckel's diverticulum; and phimosis. Cultures of the heart's blood were negative.

Histologic sections showed a dense accumulation of lymphoid cells in the periportal spaces of the liver and in the interstitial substances of the kidneys. The normal architecture of the lymph nodes was lost; the germinal centers were very actively hyperplastic, consisting of a central area of large vesicular reticulum cells and large lymphocytes surrounded by a wide zone of small lymphocytes with irregular nuclear outlines. In the spleen the malpighian corpuscles showed active hyperplasia. Here, too, the center of the germinal center consisted of reticulum cells, large lymphocytes, and a large number of disintegrated cells and nuclear débris surrounded by a dense zone of small lymphocytes with an irregular or wrinkled nuclear wall. Except in the crowded peripheral zone of the follicles, the predominating cell type was the medium-sized lymphocyte with a vesicular nucleus, one or two nucleoli, a thin cell wall, and small chromatin particles. Reticulum cells of the pulp were not unusually prominent. A few neutrophilic and eosinophilic myelocytes were scattered among the lymphoid cells. Phagocytes containing ingested débris were not frequent. No evidence of erythropoiesis was present. The bone marrow of the rib was grossly red; microscopic sections showed that it was densely cellular and that the predominating cell type was a small lymphoid cell with a heavy although irregular nuclear outline and a narrow rim of nongranular basophilic cytoplasm. Sparsely scattered among the masses of lymphoid elements were a few neutrophilic and more eosinophilic myelocytes, while mature polymorphonuclear neutrophiles, eosinophiles, and erythroid elements were scarce. Few megacaryocytes and reticulum cells were seen; phagocytes containing ingested débris were present in each microscopic field, numbering approximately 1 per cent of the cellular elements.

In Group III there were twelve cases—the remaining 30 per cent of the series. These present the most striking clinical picture as well as the most serious problems in diagnosis because of the prolonged course, the high percentage of antecedent infections, the occurrence of remissions and exacerbations, and the marked fluctuation in the blood picture. It is a slightly older group, the average age being 5.4 years. The youngest child was eighteen months, and the oldest, twelve years. Ten of these twelve ran a course of from five to ten months; one, a course of less than two months; and one, of more than three years.

Six of the twelve patients gave a history of an antecedent infection, as follows: scarlet fever in one case, severe throat infection in two, upper respiratory infections with suppurative otitis media in one, adenitis in one, and "rheumatic" joint symptoms in one. Two of the twelve gave histories of repeated upper respiratory infections, but a definite relation between the illness and the onset of leucemic symptoms could not be determined. Four had been in apparent good health previously.

In general, the story was that of a single or repeated infection, most commonly of an upper respiratory type, followed by a latent period in which there was a lack of normal vigor, a gradual onset of fever and anorexia, and a rather rapid development of extreme pallor, ecchymoses in the skin, lymphadenopathy, and a period of leucemic leucocytosis with a hypochromic anemia and thrombopenia. Apparently independent of therapy, a remission was initiated by a drop in the immature leucocytes in the peripheral blood, a diminution in the size of the spleen, a rise in the granulocyte, reticulocyte, and red blood cell counts. The remission was of varying duration and completeness. In some of the cases the clinical and hematologic recovery seemed complete for several weeks. In the cases which were under close enough observation to have interim blood counts, an exacerbation was anticipated by an elevation of the leucocyte count and of the total lymphocyte count with the reappearance of immature lymphocytes, followed either by a sustained leucemic leucocytosis or a leucopenia, hypochromic anemia, and thrombopenia, with the clinical findings of fever, lymphoid enlargement, and purpuric manifestations.

In three of the twelve cases, a prolonged early period of leucopenia, with few blast forms, together with a definite history of a recent infection, made the diagnosis during the early phase especially difficult. Such are cases 26 and 36 reported later in the paper.

In the remaining nine, the diagnosis during the early period was aided by the presence of immature leucocytic elements, although they were in some instances present only for short intervals. In general, the percentage of stem cells in the peripheral blood paralleled fluctuations in the total lymphocyte count (Chart 2). The frequent occurrence of suppurative infection during the course of leucemia is well known, but in some of these cases one was led to question seriously whether the infection might not be causative rather than concurrent, such as in cases 31 and 37.

CASE 37.—J. H., a three-and-one-half-year-old girl of German extraction, was admitted on July 17, 1933, and was under observation in the hospital or out-patient department until her death in November, 1933.

The child had been well until six weeks prior to admission, when she developed fever and lassitude without obvious cause. This lasted several days, after which

she appeared well for three weeks, when the fever recurred and she began to perspire freely and to be pale and listless. She occasionally complained of abdominal pain.

Examination at this time revealed a feverish, markedly pale child who appeared chronically ill, drowsy, and mildly toxic. Purpuric spots from 1 to 2 cm. in diameter were present on the legs and thighs; no petechiae were found on the skin or mucous membranes, but the tourniquet test was positive. The cervical and submaxillary lymph nodes were the size of large beans and discretely palpable; the axillary and inguinal nodes were smaller. The spleen was hard and very large, extending two fingerbreadths below the umbilicus and anteriorly, to the midline. The liver reached two fingerbreadths below the right costal margin. The heart and lungs were negative, and reflexes were normal. The blood showed a marked leucopenia and also an aplasia of the other blood elements. The counts were: erythrocytes, 2,030,000; hemoglobin, 30 per cent; leucocytes, 1,400, with 18 per cent neutrophiles, 12 per

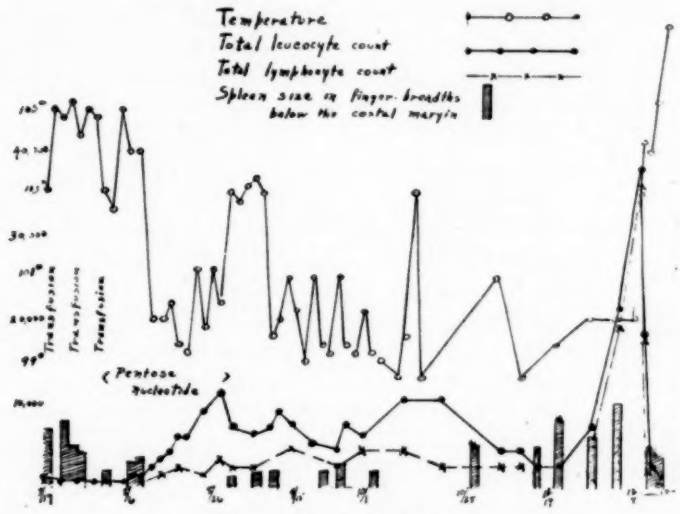

Chart 1.—J. H. (Case 37).

cent of which showed marked toxic granulation, 22 per cent small lymphocytes, 56 per cent immature lymphocytes, and 4 promyelocytes. The immature lymphocytes were the size of medium-sized lymphocytes with a large nucleus with a fairly coarse chromatin pattern, from two to four prominent nucleoli, and a narrow rim of nongranular cytoplasm. In a few, azurophile granules were present. They showed no positive oxidase granules. The platelets were markedly reduced in number. No nucleated red cells were seen, and the erythrocytes showed a marked degree of achromia. Bleeding time was 13 min. The subsequent blood findings are given in Table II and Chart 1.

Following three transfusions given at four-day intervals, the granulocyte count increased, the lymphoid cells decreased, and the spleen decreased in size. The total count remained low, and the spleen decreased in size. Nucleotide therapy was instituted. Pentnucleotide K 96 in doses of 5 c.c. was given twice daily, from July 30, 1933, to Aug. 27, 1933. During this period the total leucocytes gradually rose to 9,250, and the granulocytes numbered around 65 per cent. Together with the rise in

TABLE II

BLOOD FINDINGS ON PATIENT J. H. (CASE 37). LYMPHATIC LEUCEMIA

DATE (1933)	HEMOGLOBIN	RED BLOOD CELLS	WHITE BLOOD CELLS	PLATELETS*	DIFFERENTIAL COUNT												
							NEUTROPHILES					LYMPHOCYTES					
					BASOPHILES	EOSINOPHILES	MYELOCYTES	JUVENILES	STABS	SEGMENTEDS	TOTAL NEUTROPHILES	SMALL	MEDIUM	IMMATURE	TOTAL LYMPHOCYTES	MONOCYTES	NUCLEATED RED CELLS
July 17	30	2.03	1,400	70,000			4 myeloblasts 6		12		18	22		56	78	4	
				1 per			Transfusion 230 c.c. blood										
21	24	1.40	800	1,000 R.B.C.			4	6	12	4	26	26	46	2	74		
22	28	1.70	600	20,000													
24	25	1.60	800	30,000													
							Transfusion 150 c.c. blood										
25	28	1.75	900	40,000					4	16	20	16	56	8	80		
28	25	1.70	750	30,000				12	12	24	48	41	8	1	50	2	
29	24	1.95	750				4	6	10	32	52	40	2		42	6	
							Transfusion 150 c.c. blood										
							Pentose nucleotide 10 c.c. daily begun										
Aug. 1	22	1.80	800	46,000				5	10	45	60	35	5		40		1.8
5	25	1.50	500	25,000				4	20	64	86	12	2		14		3.0
7	25	1.70	1,300														
8			1,100														
9			1,200	30,000				1	38	28	67	28	4	1	33	0	3.2
11			17,000								60				40		
12			2,400														13.8
15	43	2.46	3,350								69				28	3	
16	43		4,100														
18	43	2.70	6,050	110,000					42	22	64	35			35	1	16.0
20		2.49	6,250														
24	48	3.50	9,250														
28		3.20	11,200				Pentose nucleotide discontinued										

TABLE II—CONT'D

DATE (1933)	HEMOGLOBIN	RED BLOOD CELLS	WHITE BLOOD CELLS	PLATELETS	DIFFERENTIAL COUNT													NUCLEATED RED CELLS
							NEUTROPHILES					LYMPHOCYTES						
					BASOPHILES	EOSINOPHILES	MYELOCYTES	JUVENILES	STABS	SEGMENTEDS	TOTAL NEUTROPHILES	SMALL	MEDIUM	IMMATURE	TOTAL LYMPHOCYTES	MONOCYTES		
Aug. 31	50	3.96	7,500			1	2	3	24	34	63	24	2	4	30	7		
Sept. 5	46	3.75	6,600			1			47	17	64	27	6		33	2		2.2
9			7,200															
11			9,200															
14			7,650			2			26	6	32	60	2		62	4		
19	54	3.40	5,250															
25	64		4,950			3					45				52			
27			7,800															
Oct. 1	68		6,750			5			9	45	54	41			41			
11	74	4.10	10,850								56				31	3		
20	72	4.82	10,200															
28	72	4.60	10,500					2	46	16	64	31			31	5		
Nov. 3	70	5.02	4,900			1			48	4	52	24	21		45	2		
8			4,500			1					18				74	7		
12	70	4.80	2,900															
24	59	4.77	8,950															
Dec. 1	59	4.80	21,750						8	1	9	84	7		91			
6			38,000			1					1	95				3		
7		2.78	18,350								2	98						
9	60		3,600			2			2	0	2	91	4		95	1		
11	60	2.42	1,200	Rare					6	8	14	81	4	1	86			

leucocytes, the red cells and platelets increased. During this period she developed bilateral otitis media, an induration of the soft tissues of the lower right leg, and inguinal adenitis. A pelvic abscess formed and ruptured into the vagina on August 30, and a second attack of inguinal adenitis resulted in suppuration and was drained on September 5. From all of these abscesses *Staphylococcus aureus* was obtained in pure culture. Following this, the leucocyte count remained between 8,000 and 10,000, with an absence of immature lymphoid forms, and the red count rose to 5,000,000. The spleen remained about two fingerbreadths below the costal margin. She was followed in the dispensary from October 15 to December 5. She was fairly well for about two weeks following discharge from the hospital, and then developed a fever and a flat maculopapular eruption on the chest and abdomen. These areas were slightly raised, dull red, faded on pressure, and were thought to be leucemic infiltrations into the skin. However, a week later they had disappeared. At this time the total count had dropped to 4,500. By November 15, she complained of severe joint pains in the elbows and knees. These joints were not swollen or red but were extremely painful on motion. After this the cervical and submaxillary lymph nodes increased in size, and the spleen again enlarged. The leucocyte count rapidly rose from a low point of 2,900 to 38,000, and the increase was in the lymphoid element. An anemia developed rapidly, and the child had difficulty in breathing before death. She had no terminal hemorrhagic symptoms or necrosis of the throat. In the week before death the leucocytes dropped rapidly from 38,000 to 1,200, and the spleen receded rapidly from the level of the umbilicus to the costal margin.

In this case the diagnosis of lymphatic leucemia in a leucopenic phase was made chiefly on the basis of the great enlargement of the spleen and lymph nodes, together with the immature lymphoid forms in the blood. With the rapid diminution in the size of the spleen following transfusions and nucleotide therapy, and the favorable response on the part of the bone marrow as shown by the increasing red count, and the high percentage of mature neutrophiles together with the evidence of localizing infections, it was hoped that the process was of an infectious nature. The joint pains, without leucemic changes in the bones, the skin eruptions, probably of a toxic nature, and the absence of late hemorrhagic manifestations are unusual.

The necropsy findings were as follows: lymphatic leucemia, lymphatic infiltrations of liver, bone marrow, kidneys, spleen, lymph nodes, and intestinal lymphoid structure; generalized pallor; infarcts of the spleen; hemorrhages in the skin, epicardium, lungs, and stomach; ulcers of the jejunum; arteriosclerosis of the aorta; ascites, malnutrition. Sections of a mesenteric lymph node showed a complete loss of normal markings so that the node had a homogenous appearance, with the sinuses distended by lymphoid cells. Some of the germinal centers could still be demarcated from the substance of the node and were seen to be markedly hyperplastic. Reticulum cells were not prominent except immediately beneath the capsule where they appeared actively proliferative. Many phagocytes containing ingested erythrocytes and intact well-stained lymphocytes were frequent in the pulp of the node.

In the section of the spleen studied, there was a fresh hemorrhagic infarct. The splenic sinuses were almost empty, but the pulp contained a greatly increased number of lymphoid cells. The malpighian corpuscles were not prominent because of the diffuse cellularity of the pulp. Groups of dense accumulations of lymphoid cells were separated by areas of large vesicular cells with vacuolated cytoplasm. Phagocytes were prominent.

The bone marrow was hyperplastic with marked proliferation of the lymphoid cells. A few myelocytes and megacaryocytes were present, as well as a few islands of erythropoiesis. Mitotic figures were seen among the lymphoid elements. The reticular cells were not unusually prominent.

CASE 31.—M. S., a two-year-old girl of Polish parentage, was admitted Feb. 2, 1923, and hospitalized until her death five months later. The illness dated from an upper respiratory infection two months prior to admission, followed progressively by weakness and pallor. For two weeks before entry she had been drowsy and feverish, and the gums had bled easily. The past history was essentially negative.

The significant physical findings on admission were those of extreme pallor, generalized lymphadenopathy, and enlargement of the liver to two fingerbreadths below the costal margin and the spleen, to the level of the umbilicus. The gums bled easily. A few petechiae but no ecchymoses were present in the skin. A hemic heart murmur was heard. The blood findings were: hemoglobin, 14 per cent; erythrocytes, 730,000; leucocytes, 8,050; platelets, 63,000. The differential count

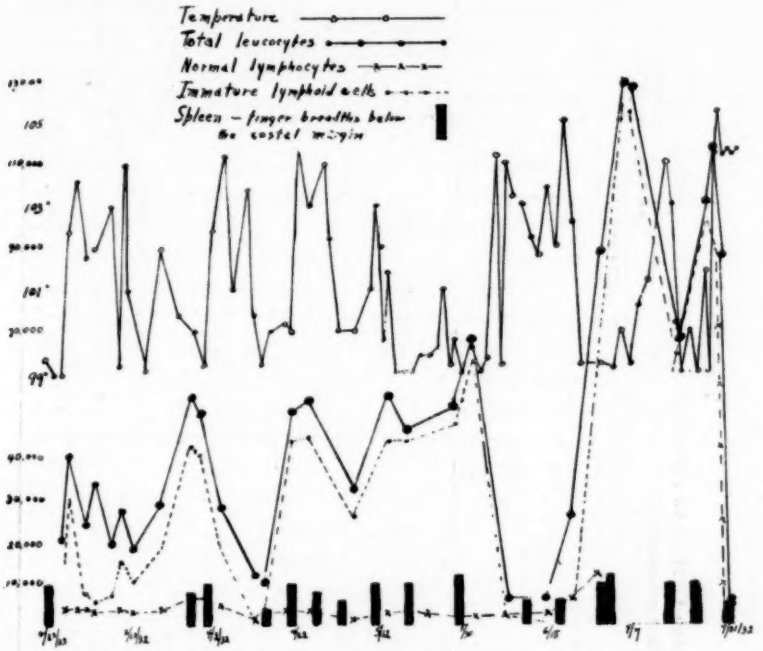

Chart 2.—M. S. (Case 31). Graph showing the relationship of the size of the spleen to the number of immature lymphoid elements in the peripheral blood.

was: polymorphonuclear neutrophiles, 19 per cent; small lymphocytes, 71 per cent; immature lymphoid cells, 4.5 per cent; monocytes, 4.5 per cent. The red cells showed 10 nucleated forms per 100 leucocytes. The coagulation time was four minutes and the bleeding time, twenty minutes. The subsequent blood findings are charted in Table III, and Chart 2 shows the relationship between the total leucocyte count, the total lymphocyte count, and the size of the spleen.

The prolonged course was characterized by an intermittent fever of a septic type, periods of leucocytosis in which large numbers of immature blast forms were found together with an enlargement of the spleen and large peripheral lymph nodes, and periods of leucopenia, at which time only few immature lymphoid cells were seen in the peripheral blood and the spleen was reduced in size. Chart 2 shows this constant parallelism between the size of the spleen and the peripheral lympho-

TABLE III

BLOOD FINDINGS ON PATIENT M. S. (CASE 31). LYMPHATIC LEUCEMIA

DATE (1923)	HEMOGLOBIN	RED BLOOD CELLS IN MILLIONS	WHITE BLOOD CELLS	PLATELETS	DIFFERENTIAL COUNT											NUCLEATED RED CELLS
					BASOPHILES	EOSINOPHILES	NEUTROPHILES					LYMPHOCYTES				MONOCYTES	
							MYELOCYTES	JUVENILES	STABS	SEGMENTED	TOTAL NEUTROPHILES	SMALL	MEDIUM	IMMATURE	TOTAL LYMPHOCYTES		
Feb. 23	14	0.73	8,050	136,000			1.5	3.0	12.0	2.5	19.0	72.0	4.5		76.5	4.5	20.0
26							3.0	7.0	2.5		12.5		87.5		87.5		7.0
27	19	0.75	20,000	130,000			3.0	2.0	3.0	2.0	10.0	23.0		67.0	90.0		5.0
29							1.0	0	3.5	1.5	6.0	17.0	25.0	52.0	94.0		
Mar. 1								3.0	3.0	1.0	7.0	9.0	18.0	76.0	93.0		5.0
3	42	2.05	13,900					1.0	6.0	3.0	10.0	27.0	1.0	60.0	88.0	2.0	
5	38	2.80		1 per 95 R.B.C.		0.5	7.5	6.5	10.0	3.5	27.5	15.5	11.5	45.0	72.0		6.5
8	48	2.51		1 per 400 R.B.C.			3.0	3.0	24.0	3.0	33.0	12.0	5.0	50.0	67.0		3.0
11	50	2.43					0.5	7.0	11.5	2.0	21.0	11.5	2.5	62.0	76.0	2.0	3.0
14	42	2.38							6.0	15.0	21.0	14.0	2.0	62.0	78.0	1.0	
21	45		29,000	60,000			2.0	5.0	3.0	14.0	24.0	6.0	8.0	62.0	76.0		
25	40	2.13	46,400														
28	40	2.00	55,800					1.0	6.5	0.5	8.0	11.5	1.0	79.5	92.0		6.0
31	30		51,050					4.0	2.0		6.0	9.0	5.0	80.0	94.0		
April 5	25		27,450				4.0			16.0	20.0	17.0		61.0	78.0	2.0	
12	30	1.45	7,350	30,000			10.0	6.0	23.0	4.0	43.0	31.0		26.0	57.0		
15	38	1.56	10,250	50,000			7.0	15.0	9.0	1.0	32.0	36.0		30.0	66.0	2.0	6.0
22	26	1.94	50,550					.	4.0	2.0	6.0	7.0		87.0	94.0		3.0
26	30	1.94	83,500			1			3.0	3.0	6.0	6.0		87.0	93.0		7.0
30			6,000			1	3.0	10.0	8.0	13.0	34.0	0		65.0	65.0		

TABLE III—CONT'D

DATE (1923)	HEMOGLOBIN	RED BLOOD CELLS IN MILLIONS	WHITE BLOOD CELLS	PLATELETS	DIFFERENTIAL COUNT												
							NEUTROPHILES					LYMPHOCYTES					
					BASOPHILES	EOSINOPHILES	MYELOCYTES	JUVENILES	STABS	SEGMENTEDS	TOTAL NEUTROPHILES	SMALL	MEDIUM	IMMATURE	TOTAL LYMPHOCYTES	MONOCYTES	NUCLEATED RED CELLS
May 7	27	1.39	32,850					10.0	11.0	4.0	25.0	4.0	13.0	56.0	73.0	2.0	11.0
12	20	1.37	55,300														
16	25	1.84	60,850														
20			46,750														
31	31	1.99	52,000				1.5			2.0	3.5	2.5		94.0	96.4		3.0
June 3			68,050						4.0	2.0	6.0			94.0	94.0		
11	18	1.22	6,500			1		1.0	20.0	10.0	31.0	30.0		38.0	68.0		6.0
14			4,900				1.0	4.0	30.0	2.0	37.0	59.0		3.0	62.0	1.0	
18	10	0.73	6,500				2.0	11.0	26.0	13.0	52.0	45.0		3.0	48.0		3.0
20	28	1.77	5,450		6			14.0	36.0	6.0	56.0				38.0		
24	30	1.50				1	3.0	7.0	22.0	1.0	33.0	30.0		36.0	66.0		1.0
30	32	1.72		1 per 50 R.B.C.		1	0	4.0	13.0	5.0	22.0	13.0		64.0	77.0		5.0
July 8	34	1.61	128,000														
14	30	1.51	83,000														
19	25	1.42	68,000	50,000							6.0				94.0		
24	22	1.15	104,000	70,000							2.0				98.0		
28	34	1.80	84,300								2.0				98.0		
30	22	1.20	5,150	8,000							2.0				98.0		

cyte count. At each period of leucopenia the spleen shrank in size, to increase again with the increase in the total count. There was no constant relation to the temperature and the leucocyte curves, nor was there any evidence that the transfusions or intermittent infections paralleled the leucocyte reaction. From March until May the picture was that of a moderately ill child with a daily fever of from 101 to 103° F., presenting purpuric manifestations, a leucocyte curve which varied from 6,000 to 55,000, and a hypochromic anemia. From May until August she was more acutely ill, and intercurrent infections, an otitis media and a dacrocystitis, occurred. At one time a marked enlargement of the submaxillary, a preauricular, and lacrymal glands presented a typical Mikulicz syndrome. X-ray evidence of sinusitis or mastoiditis was negative. Bronchopneumonia terminated the course.

A word may be said about the predominating cell type during periods of leucocytosis. This was a lymphoid cell, one and a half to two times the diameter of an erythrocyte, containing a large round or slightly oval nucleus with a fine chromatin pattern, and from three to five nucleoli. The narrow rim of rather deeply basophilic cytoplasm contained azurophile granules, but no specific granules were present, and the cells gave a negative oxidase reaction. With supravital stain these cells had from eight to fifteen neutral red bodies, an irregular nuclear outline, and a few mitochondria. When grown in tissue culture, it could not be determined that specific granules developed in vitro. The possibility that the cells were myeloblasts arises chiefly because of the constant presence of a few myeloid elements in the peripheral blood.

The necropsy findings were briefly as follows: lymphatic leucemia, leucemic infiltration into the kidneys, liver, cardiac muscle, spleen, and lymph nodes; hypertrophy of the lymph nodes and spleen; subpleural and subpericardial hemorrhages; submucous hemorrhages into the stomach, cecum, and appendix; cortical and subcapsular hemorrhages into the kidneys and destruction of the tubules; hepatomegaly with subcapsular hemorrhage; hemorrhagic pustules on the face and buttocks; marked emaciation; dilatation of the right heart and pulmonary artery, hypertrophy of the left heart; bilateral bronchopneumonia and right upper lobar pneumonia. Cultures of the heart's blood grew *Staphylococcus aureus* in pure culture.

The lymph nodes showed a thickening of the capsula, with an increase in the fibrous substance of the stroma, and a complete loss of the normal markings of the cortex and medulla. The germinal centers were indistinguishable from the rest of the cellular pulp although the cells were not so compact as to obscure the active reticulum cells. Phagocytes containing ingested débris and lymphoid cells with normal staining properties were frequently seen. A few myelocytes were found among the lymphoid cells of the pulp.

The spleen showed marked fibrosis of the capsula and reticular stroma. The thickened blood vessels of the malpighian corpuscles were surrounded by a dense layer of lymphoid cells which extended into the pulp. Between the hyperplastic centers were areas of hemorrhage and collections of lymphoid cells, a few myelocytes, and erythrocytes. Unfortunately, a section of the bone marrow was not taken. The liver and kidneys showed a marked degree of cellular infiltration about the vessels.

CASE 26.—P. Y., an Armenian boy two years of age, was admitted June 2, 1931, with a history of having been well until he developed scarlet fever four months previously, following which an enlargement of the cervical lymph nodes persisted for six weeks. This disappeared and recurred at intervals during the ensuing months, and at such periods he was feverish, ill, and pale. A yellowish pallor was noted by the mother during the two weeks prior to admission. Two days before entry the right ear began to discharge.

TABLE IV

BLOOD FINDINGS ON PATIENT P. Y. (CASE 26)

DATE (1931)	HEMOGLOBIN	RED BLOOD CELLS	PLATELETS	WHITE BLOOD CELLS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONOCYTES	EOSINOPHILES	BASOPHILES	COAGULATION TIME	BLEEDING TIME	REMARKS
June 2	15	0.90		6,300	5	95	0					Transfusion 190 c.c. blood.
2		1.47	220,000							15 min.		
4		1.53		2,400	3	94	1	1	1	10 min.	6.5 hr.	0.5 reticulocytes.
6		1.66		2,300								Transfusion 300 c.c. blood.
8	40	2.30		1,800	10	90						
10				3,200	8	92						
15		3.17		7,650	11	84	2	3				June 18: 0.12 gm. adenine sulphate intravenously.
24	43	1.40		2,100	2	98						
25				3,000	1	99						0.12 gm. adenine sulphate intravenously.
26		1.50		4,000	3	93	4					0.12 gm. adenine sulphate intravenously.
27			100,000	3,500	4	93	3					0.12 gm. adenine sulphate intravenously.
29				3,100	1	99						0.12 gm. adenine sulphate intravenously.
July 6		1.70	20,000	10,600	4	96						
10				30,300	2	98						50 c.c. blood intramuscularly
13				65,000	1	99						
16	17	0.98	5,000	73,000	1	99						

Examination on admission revealed an acutely ill boy of two years with a lemon-yellow pallor and purpuric lesions on the lower extremities; there was a purulent discharge from the right ear; the anterior and posterior cervical lymph nodes were enlarged, with a mass the size of a walnut on the left. The mucous membranes of the mouth and throat were pale; no petechiae or inflammation were present. The liver and spleen were just palpable. The blood count on admission was: erythrocytes, 900,000; leucocytes, 6,000; hemoglobin, 15 per cent; platelets, greatly reduced; lymphocytes, 87; monocytes, 8; polymorphonuclear neutrophiles, 8. Subsequent counts are given in Table IV. It was felt at the time that this was an aplastic blood picture due to an infection.

A transfusion was given shortly after admission and repeated four days later. After the first transfusion he rallied and appeared alert and comfortable for a

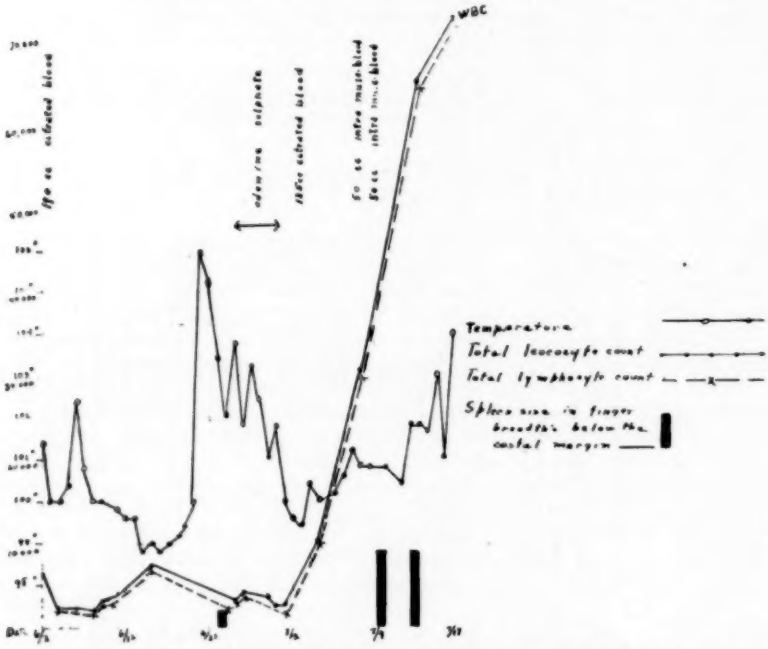

Chart 3.—P. Y. (Case 26). Graph showing the relationship of the size of the spleen to total lymphoid and the total leucocyte counts.

period of three weeks, during which time his fever ranged from 99 to 100° F.; the total red and white counts improved; and there was an increase in the granulocytes and platelets. However, the liver, spleen, and superficial lymph nodes slowly but gradually grew larger. The total leucocyte and red cell counts then began to drop, and the fever rose daily to 102° F. Bleeding of the gums and purpuric areas developed, and the right ear again discharged. At this time blood cultures showed a pure culture of *Staphylococcus albus*. For a ten-day period the leucopenia or neutropenia persisted, during which time he was given adenine sulphate intravenously, with no elevation in the granulocytes or total counts.

During the last ten days the total count increased rapidly to 73,000, and immature lymphoid forms appeared in large numbers in the blood. Petechial and

purpuric areas were constantly present. No ulceration of the mouth, throat, or mucous membranes, or hemorrhages occurred. The liver and spleen increased to four fingerbreadths below the costal margin. The child was taken home against advice the day before he died. No postmortem examination was obtained.

CASE 36.—M. G., a twelve-year-old American girl, was admitted on four occasions between May and October, 1933, with a diagnosis of leucopenia of unknown origin. After a course of five and a half months of illness characterized by repeated attacks and remissions, a typical leucemic picture developed.

During the first stay in the hospital it was felt that the condition was a neutropenic response to an infection. With the occurrence of a large number of immature lymphocytes and leucocytosis with the second attack, the leucemic process was sus-

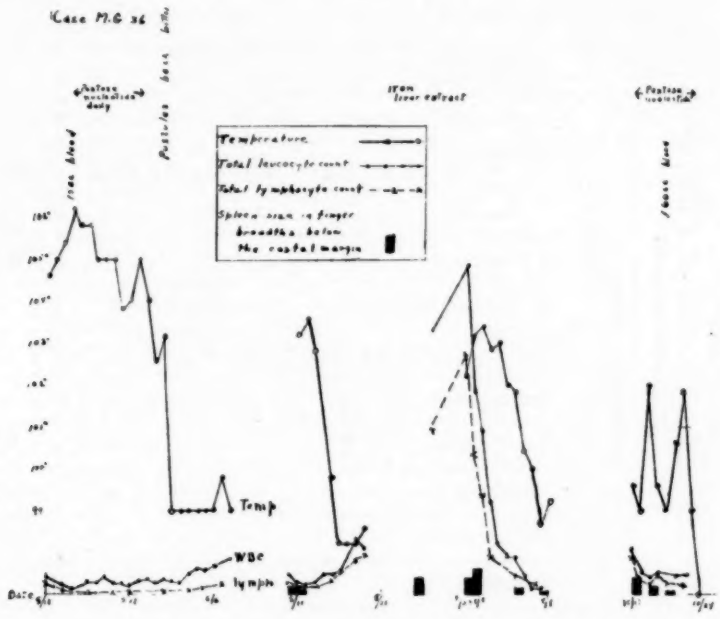

Chart 4.—M. G. (Case 36). Graph showing the relationship of the size of the spleen to the total lymphoid and the total leucocyte counts.

pected although the rapid recovery suggested a compensatory mechanism on the part of the hemopoietic system. It is noteworthy that in this case the terminal phase was an aleucemic one and that the immature lymphoid forms were present only during the phase of leucocytosis.

The onset dated from a throat infection occurring six weeks prior to the first admission in May, following which she remained weak, lost weight rapidly, and became progressively pale. On admission to the hospital the outstanding findings were those of extreme pallor, and a fever of 105° F. There were no evidences of purpura or lymphadenopathy. The blood findings were: erythrocytes, 2,800,000; hemoglobin, 43 per cent; leucocytes, 2,000; the differential count, 60 per cent lymphocytes, 24 stab neutrophiles and 26 segmented neutrophiles, with a marked reduction in the platelets (Table V). Shortly after admission a transfusion was

TABLE V

BLOOD FINDINGS ON PATIENT M. G. (CASE 36)
LYMPHATIC LEUCEMIA

DATE (1933)	HEMOGLOBIN	RED BLOOD CELLS	WHITE BLOOD CELLS	TOTAL LYMPHOCYTES	DIFFERENTIAL COUNT											NUCLEATED RED CELLS	BLEEDING TIME	REMARKS
					BASOPHILES	EOSINOPHILES	NEUTROPHILES					LYMPHOCYTES				MONOCYTES			
							MYELOCYTES	JUVENILES	STABS	SEGMENTEDS	TOTAL NEUTROPHILES	SMALL	MEDIUM	IMMATURE	TOTAL LYMPHOCYTES			
May 19	43	2.80	2,000	1,200							40	60			60			
19			1,200	840							30	70			70			
20											44	56			56			
23			1,400	140							90	10			10			
25			1,050	252					16	58	74	24			24	2		
27	45	2.31	1,000	200							72				26	2		
31			1,750	290														
June 3			2,450	960							48				44	8		
7	60	3.62	3,100	1,364							50				44	6		
10	95	5.90	2,300	1,380							40				60			
Aug. 11			1,450	1,043					10	14	24	70	2		72	4		Platelets 6 per 100 R.B.C. No abnormal or leucemic forms. Platelets 90,000.
13			1,600	1,056							31	66			66	3	0.13	
									24	4	28	72			72			
15			2,150	1,247							42				58			
								1	16	20	37	58	4		62	1		
18	92	4.95	6,850	4,100							36				60	4	0.1	No toxic changes in neutrophiles. Platelets 155,000.
25			31,450	19,184				1	21	4	26	27	23	18	68	6		
30	82	5.11	39,500	28,035				1			22				71	6		Platelets 65,000.
31			19,800	16,830			1	4	8	2	15	1	14	70	85			

TABLE V—CONT'D

DATE (1933)	HEMOGLOBIN	RED BLOOD CELLS	WHITE BLOOD CELLS	TOTAL LYMPHOCYTES	DIFFERENTIAL COUNT											NUCLEATED RED CELLS	BLEEDING TIME	REMARKS
					BASOPHILES	EOSINOPHILES	NEUTROPHILES					LYMPHOCYTES						
							MYELOCYTES	JUVENILES	STABS	SEGMENTEDS	TOTAL NEUTROPHILES	SMALL	MEDIUM	IMMATURE	TOTAL LYMPHOCYTES	MONOCYTES			
Sept. 1			11,900	11,186					9	1	10	35	42	13	90				
2			6,350	4,508							20				76	4			
3			4,850																
5			2,500	2,350			2		3		5	10	80	4	94	1	0.1	1 min.	Platelets 170,000.
6			1,750																
7			1,750	1,470							12				84	4			
Oct. 17	10	0.80	5,300	4,452	0.5		1		5	8.5	15	84			84				Lymphocytes—compact nucleus, few with cytoplasm vacuolated.
18		0.58	2,900	1,815			4	6.5	7	20	37	62	5	3	62.5				Platelets reduced. 3 immature lymphocytes.
19		0.80	2,300	1,196			2	12	19	11	44	52			52	4			
20		0.67	2,800	2,128				6	6	12	24	76			76				
21		1.00	2,250	1,305				2	22	18	42	58			58				Small to medium lymphocytes with compact nucleus.
22																			Narrow rim of basophilic cytoplasm; neutrophilic granules irregular, marked achromia and anisocytosis of R.B.C.
23		0.80	2,450	1,176				6	42	4	52	48			48			20 min.	Platelets 70,000.

given; nucleotide therapy was begun and continued for twelve days. After a febrile period of two weeks with a daily temperature of 105° F., a generalized furunculosis developed, and the temperature dropped by rapid lysis to normal. The leucocyte count rose to 4,000, and the red blood cells to 3,600,000 at the time of dismissal on June 8. On July 1 the leucocyte count was 7,000, and by August 1 she had gained fourteen pounds in weight and seemed in excellent health. About August 5 the symptoms of weakness, fever, leucopenia recurred, this time accompanied by enlargement of the cervical lymph nodes and spleen. At the time of the second admission the leucocyte count was 1,100, but on the fourth day of the hospital stay it began to climb spontaneously and on dismissal eight weeks later was 6,856, and the lymph nodes and spleen were reduced in size. No therapy was given during this period. Two weeks later she was readmitted with the complaint of joint pains and fever of four days' duration. The spleen was then three fingerbreadths below the costal margin, there was a generalized lymphadenopathy, and purpuric and a few nodular leucemic infiltrations were present in the skin. The leucocytes had climbed to 39,000, 78 per cent of which were immature lymphoid cells. Five days later the count had dropped to 2,700 and the immature lymphoid cells to 4 per cent, together with a marked reduction in the size of the spleen and lymph nodes (Chart 4). Clinical improvement again ensued. One month later she was admitted for the last time with symptoms of marked pallor, fever, and vomiting. The clinical picture was that of large purpuric areas in the skin, marked pallor, generalized enlargement of the peripheral lymph nodes, enlargement of the liver and spleen to the level of the umbilicus, a marked anemia, with red blood cells numbering 5,800,000 and a leucopenia of 5,300 cells, of which 83 per cent were small lymphocytes. Pentose nucleotide and blood were given with no benefit. An abscess developed on the cheek, from which drained a sanguineous material; the spleen was reduced in size; and the leucocytes and red blood count dropped rapidly. The patient developed air hunger and died five and a half months after the onset of the illness.

The anatomic diagnosis based on necropsy findings was aleucemic leucemia; infiltration of lymphoid cells into the liver, spleen, and kidneys; infarcts in spleen and kidneys; cutaneous hemorrhages of right cheek with superficial abrasion; generalized pallor and emaciation.

The lymph nodes showed a loss of normal architecture, the medulla and cortex being invaded by hyperplastic cellular elements. The germinal follicles were prominent and very active, the central area consisting of large vesicular lymphocytes, reticulum cells, and nuclear débris, and the peripheral zone of small and medium-sized lymphocytes with an irregular nuclear outline and a few monocytoid forms. In the medulla were areas of hemorrhage and large phagocytes containing ingested erythrocytes and nuclear débris.

The spleen showed also a diffuse infiltration with lymphoid forms. The malpighian corpuscles resembled the germinal center of the lymph nodes, with the central area of combined proliferative and degenerative changes. The reticulum cells of the pulp were not unusually prominent. A few phagocytes were present. No areas of erythropoiesis were present.

The vertebral bone marrow was grossly bright red; microscopically it was densely cellular. Islands of small lymphoid cells were distributed between less crowded areas of accumulations of hemocytoblasts, myeloblasts, a few myelocytes, and erythroid elements. Very few mature polymorphonuclear neutrophiles or eosinophiles were seen. Phagocytes with ingested débris were scarce.

The liver showed a dense infiltration of lymphoid cells in the periportal areas, and fatty degeneration about the central vein. A similar infiltration was present in the cortex of the kidney.

DISCUSSION

The high incidence of antecedent infections in this series of cases again raises the question of the rôle which infection plays in the etiology of the disease. That in 48.7 per cent of the cases a history was obtained of an infectious illness from which the patient failed to recover normally before the advent of leucemic symptoms lends presumptive evidence that some relationship exists between infection and leucemia.

The theory of the infectious origin of leucemia gains chief support from clinicians who have noted the similarity of the clinical and pathologic picture to that of an infectious process (Turk,[7] Herz,[8] Naegeli,[9] Cabot,[10] Sternberg,[11] Baar and Stransky[5]). The observations of Ellermann[12] and Furth[13] on fowl leucosis that the disease may be transmitted by inoculation of these animals with cell-free filtrates of blood and organs of leucemic chicks are experimental evidence that the leucosis of fowls is due to an infectious agent. However, in no other experimental animal has the disease been reproduced without the introduction of living leucemic cells into the host. And although leucemoid blood pictures have been observed by several investigators[5] by inoculating animals with streptococcus and staphylococcus obtained from spleen and lymph nodes of leucemic patients, conclusive evidence of the production of a true leucemia by such experiments is lacking.

Opposed to the infective theory is the concept that the disease is a neoplasm of the organs of hemopoiesis, sponsored by Banti,[14] Hirschfeld,[15] Piney,[16] Gittins,[4] and others. The points in favor of the neoplastic theory are, briefly: (1) failure to reproduce the disease in experimental subjects or to isolate an infectious agent from leucemic blood or tissues, and (2) the similarity of the pathologic findings to those of a tumor process in the production of immature cells and the tendency to metastasize by infiltration.

The theory gains strong experimental support from the experiments of MacDowell and Richter[17] and of Furth[18] on the transmissible leucemia of mice; these investigators conclude that the disease is transmissible in mice only when living leucemic cells are injected into a susceptible host, and that the nature of the resultant growth is that of a tumor with or without a leucemic blood picture. This conflict in the experimental evidence, i.e., that the leucosis of fowls can be transmitted by inoculation with cell-free filtrates and that the chronic leucosis of mice cannot, raises the question whether the two conditions are the same and comparable. It has long been suspected[5] that the acute and the chronic leucemias are different in character, the acute leucemias having much in common with infections and the chronic forms more similarity to tumors of lymphoid or myeloid tissues.

A third concept, that a constitutional inferiority of the hemopoietic organs predisposes to an unstable response to infections, is a current one supported by Mikulowski,[19] Wolff,[20] Strumia,[21] and Burkens[22] and is suggested by the occasional occurrence of leucemia in families exhibiting other types of diseases of the blood-forming tissues, such as anemia, agranulocytosis, or infectious mononucleosis, etc. The family histories in our cases are not complete enough to warrant inferences in this regard.

The diagnosis of leucemia is made especially difficult by two conditions, notably a leucemoid response to an infection, and malignant neutropenia, perhaps better called sepsis with neutropenia.

The term "leucemoid," coined by Krumbhaar, originally applied both to conditions simulating leucemia only because of a hyperleucocytosis, and also to conditions whose resemblance to leucemia extended to the clinical and pathologic fields. When restricted to this latter group, the term conveniently describes those borderline cases, otherwise classified with difficulty. (See Case 41.) These leucemoid conditions more often simulate the hematologic picture of acute myeloid leucemia than that of the lymphatic type, probably since the ordinary infections more commonly provoke the appearance of immature neutrophiles than immature lymphoid forms. However, in spite of the fact that infectious mononucleosis usually presents a typical and characteristic cell type,[24] not infrequently cases occur in which the hematologic picture is much like that of acute lymphatic leucemia and the diagnosis must be determined by other clinical signs, i.e., the clinical course, the heterophile antigen test, and the absence of anemia and hemorrhagic manifestations.

The differentiation of aleucemic leucemia from malignant neutropenia is admittedly difficult, and, because the syndrome of "sepsis with leucopenia" is so similar to malignant neutropenia, these two conditions will bear discussion.

In 1930 Brennemann and Bigler[25] reported ten cases which represent a clinical group not easily classified with other known entities and which they called "sepsis with leucopenia." The clinical story had much in common with that of aleucemic leucemia and of malignant neutropenia; an illness of from two to five months' duration, often initiated by an upper respiratory infection, was followed by a period of anorexia, fever, progressive pallor and weakness, and an abrupt, invariably and predictably fatal terminal phase characterized by a septic fever, prostration, anemia, leucopenia affecting chiefly the neutrophiles, and hemorrhagic symptoms accompanied by a thrombopenia. The pathologic picture was that of petechial hemorrhages into the tissue, focal necroses in various organs, hyperplasia of the germinal centers of the lymph nodes and spleen with reduced cellularity of the stroma and proliferation of the reticular and phagocytic elements.

The bone marrow, while grossly red or pink, was less cellular than normal, with marked reduction in the percentage of granulocytes, erythroid elements and megacaryocytes, and some hyperplasia of the reticular and phagocytic cells. Clinically the syndrome was differentiated from agranulocytosis by the absence of necrotic lesions in the mouth and pharynx and the presence of hemorrhagic symptoms with anemia.

Malignant neutropenia or agranulocytosis, as described by Schultz,[26] is a disease which specifically affects the granulocytes and spares the erythroid lymphatic, and megacaryocytic elements of the hemopoietic system. Clinically the course is that of rapidly developing toxemia, necrosis of the mucous membranes of the pharynx and other mucous surfaces without abscess formation, marked neutropenia without a severe anemia or thrombopenia. A voluminous literature, accumulated since the original description in 1922, debates the nature of the disease as a clinical entity against that of a symptom-complex. A weight of evidence indicates that there is no essential difference between the so-called idiopathic agranulocytosis and symptomatic agranulocytosis occurring in infections and drug idiosyncrasies.

Although the classic syndrome is uncommon in children, cases have been reported by Schwarz,[27] Weiss,[28] Zahorsky,[29] Dayton,[30] Rutledge,[31] Tokue and Yasumoto,[32] Kato and Vorwald,[33] Kilduffe and Nickman,[34] and Friedman and Smith,[35] which are typical of true agranulocytosis. However, in the majority of the cases reported as agranulocytosis in children and in many of the reports of adult cases, the syndrome is not clear-cut, as hemorrhagic symptoms with thrombopenia and a severe anemia occur.

Empey and Proescher[36] describe a case of recurrent agranulocytosis in a child three and one-half years old, whose clinical course was otherwise typical but was complicated by purpuric manifestations and an anemia of a hemolytic type. The pathologic picture was typical of agranulocytosis, with focal necroses in the organs, lymphoid transformation of the bone marrow, and also some reduction in the erythroid elements and degenerative changes in the megacaryocytes. These marrow findings are typical of those which Jaffé[37] describes as the essential change in agranulocytosis, notably, a primary hyperplasia of all the myeloid elements followed by marked degenerative changes in the myelocytes and reduction in the total number of granulocytes, together with degenerative changes in the megacaryocytes, and some evidence of disturbed erythropoiesis. Degenerative changes in the megacaryocytes are also reported by Richards,[38] Rose,[39] and Dwyer.[40] Jaffé concludes from a study of nine cases, five of which were idiopathic agranulocytosis, two of which developed the syndrome during the course of antisyphiltic treatment and two during the course of a *Streptococcus viridans* septicemia, that no essential pathologic difference exists between the symptomatic and the idiopathic forms.

In view of this evidence, it would seem that the borderline, if indeed it exists, between true agranulocytosis and the syndrome of sepsis with leucopenia is a narrow one. If the current theory that a hemotoxin of either bacterial or chemical origin is the pathogenic agent is correct, it offers a logical explanation for the gradation of these syndromes one into the other.

The theory has support in experimental observations. For instance, it is known that hemotoxic agents, such as benzene, usually damage granulocytes first, and then later the megacaryocytes; that with the same hemotoxin used for different animals of the same species, the nature of the bone marrow response cannot be predicted: one cell strain will be depressed in one animal, an aplastic picture develop in another, or a stimulation of the myeloid elements in still another. Bock and Wiede[41] point out that this variety of response to the same agent is common in arsenical poisoning which occurs during antisyphilitic treatment. They report nine cases treated with neosalvarsan and bismuth, four of which developed agranulocytosis, three a depression of all the leucocytic elements (aleucie), and two a depression of all the myeloid elements (amelie).

The clinical differentiation of aleucemic leucemia from the syndrome of sepsis with leucopenia is exceedingly difficult. There is no essential difference in the cardinal symptoms; fever, lymphoid hyperplasia, variable enlargement of the liver and spleen, and hemorrhagic manifestations occur in both. Mouth lesions are not constantly present in either. Evidence of an existing infection may or may not be present in both, and whether it is an intercurrent or a causative infection is a question. Remissions occur in both, and although these are usually longer in leucemia, the final outcome is always fatal. Among the cases of sepsis with leucopenia observed, there is one clinical point that has been fairly reliable, notably the degree of toxemia. The patient appears ill, toxic, and listless, and in spite of transient improvement following transfusion, the downward trend is persistent and rapid. The aleucemic patient, except during the terminal phase, appears mentally alert although physically weak from anemia, and has a clear expression and waxy pallor. The distress is due to air hunger or to bleeding of the mucous membranes or to enlargement of the liver or spleen rather than primarily to a toxemia. The unreliability of such an observation is obvious, but when the clinical differentiation depends on such slender threads, it is at times of value.

When immature or blast forms are present during the leucopenic phase, they aid considerably in the recognition of an aleucemic process; but as in Case 34 they may be absent throughout the period of observation and there may thus be no essential difference in the hematologic picture in the two diseases.

The diagnosis can be made with certainty only when the pathologic changes are typical of leucemia. The characteristic findings, notably that of extreme proliferative changes in the organs of hemopoiesis, are essentially the same regardless of the degree of leucocytosis in the peripheral blood.

The degree of cellular infiltration into the tissues is extremely variable; in general it is most marked in cases with a prolonged course and a constant hyperleucocytosis and less marked in the rapidly fulminating cases, and also in those with a fluctuating leucocyte.

The characteristic histologic finding of lymphatic leucemia is the loss of the typical architecture of the lymph nodes, caused by the crowding of the sinusoids with recently formed lymphocytes, among which mitotic figures are frequently seen. The germinal centers are markedly hyperplastic, and the active proliferation of reticulum cells, together with the presence of large phagocytes containing both nuclear débris and cells with normal staining properties, indicate the uncontrolled process of cell production and disintegration which is characteristic of the entity. The same picture is seen in the bone marrow, where granular and erythroid elements are suppressed and supplanted by lymphoid hyperplasia. Among the myeloid leucemias of this series which came to autopsy, changes in the hemopoietic system were essentially similar to those of the lymphatic type except for the finding of myelocytes among the immature lymphoid forms. The germinal centers of the lymph nodes and spleen were hyperplastic in both; fibrosis of the spleen and lymph nodes was present in both, although not constantly; cytologic differences in the immature or blast forms in the two conditions could not be determined with certainty, and except for the occurrence of neighboring myelocytes, the diagnosis of myeloid leucemia as opposed to lymphoid leucemia could not be made.

In several cases changes in the lymph nodes similar to those in the cases of sepsis with leucopenia were found. Necrosis at the center of the germinal follicles surrounded by a zone of actively proliferating lymphocytes, active phagocytosis, and hyperplasia of reticulum cells were findings typical of both cases of leucemia and of sepsis; they were not restricted to the cases of aleucemic leucemia or to those with a prolonged period of leucopenia (Cases 36, 37, and 41). Similarities such as these lead one to consider whether the underlying pathologic change is not essentially the same in the two diseases, the pathologic picture at the time of death being dependent upon a hyperplastic response in the case of leucemia and a hypoplastic response in the case of sepsis with leucopenia. During the past two or three years, a large number of cases have been reported with an early course of agranulocytosis and a terminal picture of leucemia.[19, 21, 22] It is, of

course, difficult to determine from the reports that these were not frank cases of aleucemic leucemia from the onset. These observers point out the similarity in the hyperplastic changes in the bone marrow found in some cases of agranulocytosis to a leucemic process.

The confusion which would result from deductions as to the probable relationship between these apparently allied conditions permits of no safe speculation until further detailed pathologic studies have been made on cases that succumb at various stages of the disease.

SUMMARY

1. An analysis of forty-one cases of leucemia observed at the Children's Memorial Hospital emphasizes the similarities between childhood leucemia and a disease of an infectious nature. Forty-eight and seven-tenths per cent of the group gave a history of a known antecedent infection, preceding the onset of leucemic symptoms. The incidence of antecedent infections was highest among those cases whose early course was aleucemic.

2. Three common clinical types are discussed:

Type I, the course of which is fulminating and the clinical and the hematologic features of which are classical.

Type II, the course of which is less rapidly fatal, and the clinical and the hematologic aspects of which are more easily confused with leucemoid states or other disorders of the hemopoietic system.

Type III, the course of which is characterized by prolonged period of illness marked by the occurrence of remissions and exacerbations and a fluctuating blood picture. The aleucemic phase of this group has certain clinical and pathologic features in common with malignant neutropenia.

REFERENCES

1. Ramsay, G. W.: Arch. Dis. Child. **2**: 119, 1928.
2. Cooke, J.: J. A. M. A. **101**: 432, 1933.
3. Hunter, W. K.: Glasgow M. J. **109**: 1, 1928.
4. Gittins, R.: Arch. Dis. Child. **8**: 291, 1933.
5. Baar, H., and Stransky, E.: Die klinische Hämatologie des Kindesalters, Vienna, 1928, Franz Deuticke.
6. Mills, S. D.: J. PEDIAT. **6**: 634, 1935.
7. Turk: Quoted by Naegeli.[9]
8. Herz, A.: Die akute Leukamie, Leipzig, 1911.
9. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, 1931, Julius Springer.
10. Cabot, R. C.: Am. J. M. Sc. **145**: 135, 1913.
11. Sternberg, C.: Fathologie der Primarerkrankugen des lymphatischen und haemopoetischen Apparates, Wiesbaden, 1905.
12. Ellermann, V.: Leucosis of Fowls and Leucemia Problems, London, 1921, Gyldendal.
Idem: J. Exper. Med. **51**: 659, 1930; **52**: 823, 1930; **57**: 1, 1933.
13. Furth, J.: J. Exper. Med. **58**: 253, 1933.
14. Banti, G.: Centralbl. f. allg. path. u. path. Anat. (Ziegler) **15**: 1, 1904.
15. Hirschfeld, H.: Schittenhelms Handbuch der Blutkrankheiten, 1925.
16. Piney, A.: Brit. J. Radiol. **5**: 289, 1932.
17. MacDowell, C., and Richter, M.: Proc. Soc. Exper. Biol. & Med. **28**: 1012, 1931.

18. Furth, J.: Am. J. Cancer Research **19**: 521, 1933.
19. Mikulowski, V.: Sang. **8**: 732, 1933.
20. Wolff, E.: Folia haemat. **44**: 38, 1931.
21. Strumia, M.: Am. J. M. Sc. **187**: 826, 1933.
22. Burkens, J. C. J.: Nederl. tijdschr v. geneesk. **75**: 2722, 1931.
23. Krumbhaar, E. B.: Am. J. M. Sc. **172**: 519, 1926.
24. Downey, H.: Arch. Int. Med. **27**: 82, 1923.
25. Brennemann, J., and Bigler, J.: Am. J. Dis. Child. **40**: 515, 1930.
26. Schultz, W.: Deutsche med. Wchnschr. **48**: 1495, 1922.
27. Schwarz, E.: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. **3**: 190, 1904.
28. Weiss, J.: Wien. Arch. f. inn. Med. **14**: 303, 1927.
29. Zahorsky, J.: Am. J. Dis. Child. **35**: 436, 1928.
30. Dayton, D. M.: Northwest Med. **27**: 436, 1928.
31. Rutledge, B. H.: Bull. Johns Hopkins Hosp. **46**: 369, 1930.
32. Tokue, K., and Yasumoto, M.: Am. J. Dis. Child. **38**: 1037, 1929.
33. Kato, K., and Vorwald, J.: Am. J. Dis. Child. **44**: 556, 1932.
34. Kilduffe, R. A., and Nickman, E. H.: Am. J. Dis. Child. **47**: 1065, 1934.
35. Friedman, E., and Smith, T., Jr.: Colorado Med. **29**: 26, 1932.
36. Empey, L. N., and Proescher, F.: Am. J. Dis. Child. **43**: 947, 1932.
37. Jaffé, R. H.: Arch. Path. **16**: 611, 1933.
38. Richards, C. V.: Arch. Int. Med. **48**: 793, 1931.
39. Rose, E., and Hanssen, K.: Arch. Int. Med. **43**: 533, 1929.
40. Dwyer, H., and Helwig, F.: Am. J. Dis. Child. **35**: 1041, 1928.
41. Bock, E. H., and Wiede, K.: Folia haemat. **42**: 7, 1930.

Critical Review

DISORDERS OF INTERNAL GLAND SECRETION IN CHILDREN

FRITZ B. TALBOT, M.D.
BOSTON, MASS.

IT HAS become increasingly clear that there is an intimate relationship between the various glands of internal secretion. The pituitary gland has been discovered to be a storehouse of hormones and, in consequence, is believed to be of such importance that it plays some part in regulating important functions in almost all parts of the body. Although many advances have been made in the knowledge of the activities and physiology of the different glands, the practical application of this data has still to be worked out. With the exception of thyroxine, insulin, adrenalin, and pituitrin, there is still much to be learned in the manufacture of the various hormones. Yet reports in the literature indicate that much progress has been made in the production of preparations which are commercially available, and it is to be hoped that they will be further perfected and thus become valuable therapeutic aids to medicine.

Although it is now known that the glands are intimately related and that the action of one affects that of others, a clear picture of a clinical case cannot be obtained unless the various glands are considered separately, as well as in their relation to other glands. The writer has evolved the following table of clinical tests as they relate to gland function and it may be helpful in analyzing certain types of cases.

TABLE I

Lowered basal metabolism	Hypothyroidism Hypoadrenalism Hypogonadism
Blood chemistry	
Blood sugar	Low in insufficiency of adrenal Slightly diminished in deficiency of anterior pituitary High in deficiency of insulin
Sugar tolerance curve	Low: hypopituitary anterior, hypoadrenalism → Increased tolerance High: deficient insulin, diabetes mellitus → Decreased tolerance
Lipoids: fat curve	High in pituitary obesity Insulin causes rise Low on administration of pituitrin
Calcium	Low in hypoparathyroidism High normal after parathyroid extract
Sodium (chloride)	Low in deficiency of adrenal cortex Increased by high salt diet—cortin

Growth	
Skeleton development X-ray	Excessive in excess anterior pituitary growth hormone Diminished in dwarfism, excess pineal Gigantism plus anterior pituitary Early adolescence—thymus Retarded or stunted—lack of anterior pituitary Secondarily in hypothyroidism Pineal
Obesity Sex development	*Deficient*—pituitary and female gonad Retarded or deficient—lack of anterior pituitary, adrenal cortex, and gonads *Precocious*—excess pituitary, adrenal cortex, and gonads

With the present state of knowledge it is impossible to say which of the glands is primarily responsible for the symptoms and laboratory data enumerated. Some of these statements need further corroborative evidence before they can be accepted as absolute facts. It is quite probable that further extension of these tests to all glandular conditions may modify and increase the scope of our knowledge and its usefulness.

It is not improbable that in the final analysis all growth abnormalities will be traced back to the growth hormone (somatotropic of Evans) of the anterior pituitary, and yet today it is impossible to say whether the pineal and the thymus may not play independent parts also in regulating the rate of growth.

The regulation of heat production seems to be a function of the thyroid gland, but the thyrotropic hormone of the pituitary may be the principal regulator of this thyroid activity. The reaction of the adrenals and the gonads to the thyroid has not been clearly established in this respect. Sexual development is dependent on the pituitary hormones and seems to depend upon two gonadotropic factors, one of which stimulates the gametogenic tissues, and the other the interstitial tissues.

The mammotropic hormone of the pituitary[23] activates the mature mammary glands of the mother and seems to have a favorable influence on her attitude toward maternity. On the other hand, deficiency of the adrenal cortical hormone retards growth as well as mammary activity so that the hormones of both glands must cooperate in the development of the mammary glands. The pituitary has an adrenotropic hormone which must play an important part in the function of the adrenal. The pituitary must also have a hormone which plays an important part in the regulation of the sugar metabolism, since experimental diabetes cannot be produced in the absence of the pituitary. Of its other probable functions may also be mentioned regulation of the fat and water metabolism.

A new phase of the subject was opened by Collip[6] when he announced the discovery of antihormones which he considers "as a true hormone in every way and not as the result of an antigen-antibody response." The implications of this knowledge open up an entirely different point of view which future experiments should amplify. His experiments indicate that endocrine preparations cannot be prescribed indiscriminately since their improper use may be harmful if they upset the balance of the glandular system. Reports are now appearing in the literature in which this result has been recognized clinically.

Hoskins[15] feels that "merely to overcome a glandular deficit by substitution therapy is in principle fairly easy, but to reestablish a delicate glandular balance presents a much more difficult problem."

Thyroid Gland.—The thyroid gland is most important to the general practitioner because the thyroid hormone is very effective in treatment. Thompson and his coworkers[32] have continued their studies of the activity of thyroxine and show that the oral administration of pure thyroxine suspended in distilled water is without a definite effect on the basal metabolic rate of patients with myxedema. Crystalline monosodium salt administered by mouth increases the metabolism 7 points; an equal dose of alkaline solution 20 points, and 32 points (from minus 37 to minus 5 per cent) when administered intravenously.

It is important to remember that the various commercial preparations on the market vary in their effectiveness and reference is made to this review in the *Journal of Pediatrics*, January, 1935. All clinical records of treatment should state specifically what make of thyroid is being used.

Hoskins[15] emphasizes the fact that thyroid insufficiency may be present in children without the classical symptom of myxedema. He says, "The picture consists of moderate or slight delay in growth, teething, and skeletal development; mental retardation; dry and brittle hair; poor nutrition and sluggish functions of the skin; constipation; emotional instability, disturbed sleep, capricious appetite and intractability; painful muscles and joints, and, what is especially illuminating, failure to respond to dietary treatment." If all these symptoms must be present, this type of hypothyroidism must be rare. He feels that radiographic studies of carpal development are important in diagnosis. He is apparently skeptical of the usefulness of the cholesterol test.

Interesting data of the thyroxine reserve of the body are found in the work of Blumgart and Davis[2] who are treating chronic heart disease by complete removal of the thyroid gland. They find that the lowest metabolic rate is reached some time between the third and the ninth week after operation. Since these data can be used as a measure of the exhaustion of the thyroxine reserve of the body, it shows that in mature adults the exhaustion may be reached earlier than in infant cretins whose metabolism does not reach a low level, about minus 20 per cent, until the twelfth week. They also suggest that the mother's milk may supply a small amount of thyroxine and thus postpone the appearance of symptoms.

Bronstein and Milles[4] report the postmortem findings in two cretins with complete absence of the thyroid gland. The sketchy description of the pathologic findings of the endocrine system diminishes the value of the report. Especially to be deplored is the failure to examine the pituitary in either case.

Wells[37] reports in detail a case of dwarfism with lingual goiter and cystic hypophysis, in which the only thyroid tissue present in the body was in the lingual tissue. This is a probable characteristic of lingual goiter.

The relation of blood lipoids, fatty acid, and cholesterol to thyroid has been studied by Hepler.[14] He found that with the administration of thyroid for six to nine weeks the percentage increase of blood lipoids after a fat feeding was greater than in the normal control. On the other hand, after the discontinuation of thyroid, both the fatty acids and cholesterol increased greatly and decreased when thyroid

was again administered. Fat tolerance curves were much higher when thyroid was given again. He gives as the most satisfactory explanation the probability that the higher level of blood fat and sugar must be established and maintained at a higher level in order to sustain the increased metabolism. Such studies of the fat metabolism offer great possibilities and are necessary to clarify such questions as to the part cholesterol should play in the diagnosis of endocrine disturbances.

Toxic Goiter.—Means[21] in discussing the effect of iodine on toxic goiter emphasizes the fact "that iodine characteristically produces marked amelioration in the intensity of the thyrotoxicosis, which, however, returns to its former state if the administration of iodine is stopped." This result can be obtained at any time during the course of the disease but has no effect on the duration or direction of its progress. Irradiation brings about cure of symptoms in one-third of the cases. He recommends as treatment (mostly adults) subtotal thyroidectomy in fully iodinized subjects and has had a mortality of 0.6 per cent in ten years.

Rose, Rose and Pendergrass[24] treated a series of children with thyrotoxicosis by radiation. They felt that one of the chief objections to radiation in the past was lack of standardization of dosage. This objection has been removed by the introduction of the standard r unit which is defined as "the quantity of roentgen radiation which, when the secondary electrons are fully utilized and the wall effect of the chamber is avoided, produces in 1 c.c. of atmospheric air at 0° C. and 76 cm. of mercury pressure such a degree of conductivity that one electrostatic unit of change is measured at saturation current."[35] They conclude that although it is known that the tendency to spontaneous remission is marked in juvenile hyperthyroidism "adequate irradiation of the thyroid gland in this disease is followed sufficiently often by satisfactory permanent remission to justify a carefully controlled trial, provided that efficient apparatus is available." They recommend operation if improvement does not appear within three months.

Exophthalmic goiter is very unusual under five years of age and uncommon before puberty. Elliott[8] reports a case of a child two and one-half years old in whom the earliest symptoms suggesting the condition were first observed before the age of one year. He quotes White's case (1912) in a newborn infant; Klaus' case (1914) in a nine-month-old infant, and Helmholz' case (1926) in a baby of eleven months.

Loeb[16] has discovered two hormones in the pituitary which stimulate the thyroid. He was able to produce all the symptoms of exophthalmic goiter in animals by administering the proper pituitary hormone.

Marine's summary of "The Pathogenesis and Prevention of Simple or Endemic Goiter" in the special series of articles, "Glandular Physiology and Therapy," in the *Journal of the American Medical Association*, deserves attention, especially of those physicians living in goiter regions. He believes that "the view that goiter is caused by a specific virus or toxin or by the presence of a specific substance may be permanently abandoned and that one is justified in concluding that simple or endemic goiter is a work or compensatory hypertrophy instituted immediately by the thyrotropic hormone of the anterior pituitary in response to the demands, normal or abnormal, of the body

for thyroid secretion" and that "goiter is a deficiency disease due to an insufficient supply of iodine." This deficiency may result from abnormally high needs of iodine as at puberty, deficient absorption of a normal intake, or an abnormally low intake of iodine. Since it is in itself a summary, it will receive no further mention here, as it should be read in the original.

Bram,[8] who studied 102 cases of exophthalmic goiter in children ten years old and under, concluded that the exciting cause was focal or general infection in contradistinction to adults in whom he thought it was psychic trauma. He feels that elimination of the focus of infection with other medical procedures should effect recovery in the average child after several months of "patient teamwork."

Hellwig[13] did some very interesting work on white rats in which he was able to produce goiter by feeding them a calcium-rich diet. When the diet was poor in iodine and resultant goiters were colloid-poor and iodine-poor with low function, the addition of iodine increased their colloid and function.

Relations of the Thyroid to Other Glands.—In parenchymatous goiterous patients the anterior pituitary is enlarged. With the removal of the pituitary the thyrotropic hormone results in involution of the thyroid. This, however, is not to be recommended as a clinical procedure. The thyroid function can be reestablished in animals by administering anterior pituitary. Removal of the sex glands of animals results in involution of the thyroid. The thyroid, on the other hand, affects the sex glands as is seen in cretins who fail to develop sexually. Thyroidectomy hastens thymus involution, and in goiter there is usually enlargement of the thymus. Other glands are also affected by the thyroid, but exactly how is still unknown.

Parathyroid Gland.—There are no significant changes in opinion concerning the parathyroid gland during the past year. Its chief importance lies in its influence on the calcium and phosphorus metabolism. It is particularly valuable in acute parathyroid insufficiency following operation. Prolonged and increased dosages of parathormone have resulted in the development of antihormones thus nullifying its value. Calcium gluconate in 10 per cent solution slowly administered intravenously (20 c.c. in the adult in not less than four minutes) has been found useful to raise the calcium content of the blood temporarily. Vitamin D in amounts which do not upset the digestion has been more useful when prolonged treatment is desired.[12, 1]

Thymus.—The thymus gland seems to have at last found its place in the light. The work reported by Rowntree, Clark, Hanson, and Steinberg[23] opens a new approach to the problem and seems to have established in a brilliant manner a definite type of physiology. These workers injected intraperitoneally into rats Hanson's thymus extract and were able to breed rats whose rate of growth and development was accelerated. This acceleration became more and more pronounced in each successive generation of treated rats (carried to the fifth generation). They illustrate how successive generations of rats to whom the thymus gland was administered developed and matured earlier than the normal control rat. Striking photographs illustrate the marked increase in size. Table II illustrates the greatest change accomplished.

Pituitary.—Of the mass of literature which deals directly or remotely with the pituitary gland the "special articles" which have

TABLE II

	CONTROL ANIMALS	FIFTH GENERATION F_4
Average weight at birth (gm.)	4.6	5.6
Opening of ears (days)	2½-3½	1
Eruption of teeth (days)	8-10	1
Appearance of hair (days)	12-16	2-3
Opening of eyes (days)	14-17	2-3
Descent of testes (days)	35-40	4-5
Opening of vagina (days)	55-62	18-19
Average number per liter	4.9	10.5
Percentage of survival	37.8	57.0

been written for the *Journal of the American Medical Association* cannot be summarized here as they are in themselves summaries which have been written by authorities in the various fields and should be read in the original. They are as follows: Smith's "General Physiology of the Anterior Hypophysis"; Riddle's "The Lactogenic Factor of the Pituitary"; Geiling's "The Posterior Hypophysis"; Collip's "Diabetogenic, Thyrotropic, Adrenotropic and Parathyrotropic Factors of the Pituitary" (two articles); Novak's "Anterior Pituitary and Anterior Pituitary-Like Substances"; and Evans' "The Growth Hormone of the Anterior Pituitary."

Of clinical interest is Turner's report of the use of pituitrin, intermedin and pitmelanin in the treatment of diabetes insipidus.[34] He found that there was a reduction in diuresis and thrist in all five patients when he used intermedin but that the response was not so great as that obtained by equal amounts of pituitrin. The patients preferred intermedin and pitmelanin to other pituitary preparations because of their freedom from pressor effects. He concluded that intermedin and pitmelanin contained the antidiuretic factors of the hypophysis and are of value in controlling the symptoms of diabetes insipidus.

Webster[36] reports his experience with extracts of pregnancy urine in the treatment of eleven cases of cryptorchidism. The initial dose was 25 rat units which was given daily in increasing doses until a 250 rat unit dosage was reached. This amount was given for two weeks. In ten cases the testes descended during the course of the treatment. Cohn[5] reports three cures in four children treated.

Gardiner-Hill[10] thinks that the clinical picture of the pituitary disorders of childhood varies widely. The symptoms have some relation to the presence or absence of tumor. Preadolescent hypopituitarism, he says, shows a defect in growth with sex infantilism. Adenomas of the anterior lobe are rare. He thinks that the diagnosis is too often incorrectly made and that Fröhlich's syndrome is rare.

My survey of the literature leads me to the conclusion that Cushing's basophilic adenoma of the pituitary is a very rare condition in preadolescent childhood.

Pineal Gland.—Rowntree and his coworkers[26] made a study of the effect of pineal extract (Hanson) using the same methods pursued in the thymus studies. Most of the rats so treated appear fairly healthy but more lethargic and somnolent than the normal controls. They become more and more dwarfed in each successive treated generation. Pineal extract, therefore, seems to retard the rate of growth. It was also found to hasten the onset of adolescence.

Silberstein and Engel[30] and Saphir[29] independently discovered that the pineal body contains an estrogenic substance. The significance of these findings is yet to be determined, but they are of interest because clinically the power of producing precocious puberty has been attributed to the pineal body.

Adrenal Gland.—The physiology of the adrenal cortex has been reviewed by Loeb[17] and that of the medulla by Rogoff.[27] The latter also tested commercial adrenal extract (eschatin) and concluded that it is not yet possible to rely on the manufacture of this on a commercial scale.[28] Loeb and his associates[18] says the "successful treatment of Addison's disease will be accomplished only when the active principle or principles of the adrenal cortex becomes available for clinical use in high concentration and in a form that lies within the economic limits of the sufferers from this disorder." He found that adrenal cortical deficiency was associated with a diminished sodium in the blood which was accompanied by diminished chlorides. Feeding sodium chloride had a favorable effect on the patient. This improvement was also seen, he says, by Harrop and Snell. He feels that the sodium concentration of the blood is decreased because of increased sodium excretion.

Török and Neufeld[33] did not find that the injection of the cortical hormone in normal children had any effect on the excretion of chlorides.

Luechese,[19] as a result of experiments on rabbits, concludes that suprarenal insufficiency retards the formation of callus in fractures. It is benefited by the injection of cortical extracts. This, if substantiated, should be very helpful clinically in the treatment of fractures which do not unite.

Gonads.—Most of the knowledge concerning the gonads is more applicable to adults than children. The problems which arise at puberty are as yet little understood and should be investigated from many angles before any sound scheme of treatment can be evolved.

The use of the estrogenic hormone in the treatment of gonorrheal vaginitis of children is still under investigation and seems to promise a valuable, if not completely, curative method of treatment of this disorder. It is probable that application of the hormone to the vaginal mucosa will effect the best results.

The use of pregnancy urine in the treatment of undescended testes has been discussed in an earlier section.

The interrelation of the gonads and the other glands is being intensively studied and although it is difficult to construct any system which will help the clinician, each year new data are gradually clearing up many important points.

REFERENCES

1. Aub, J. C.: Parathyroid Hormone Therapy, J. A. M. A. **105**: 197, 1935.
2. Blumgart, H. L., and Davis, D.: Hypothyroidism Induced by Complete Removal of the Normal Thyroid Gland in the Treatment of Chronic Heart Disease, Endocrinology **18**: 693, 1934.
3. Bram, I.: Pennsylvania M. J. **37**: 45, 1933.
4. Bronstein, I. P., and Milles, G.: Hypothyroidism and Cretinism in Childhood: IV. Postmortem Reports on Two Cretins, Am. J. Dis. Child. **49**: 1564, 1935.
5. Cohn, S.: Anterior-Pituitary-Like Principle in the Treatment of Maldescent of the Testicle, J. A. M. A. **103**: 103, 1934.
6. Collip, J. B.: Recent Studies on Anti-Hormones, Ann. Int. Med. **9**: 150, 1935.
7. Collip, J. B.: Diabetogenic, Thyrotropic, Adrenotropic and Parathyrotropic Factors of the Pituitary, J. A. M. A. **104**: 827 and 916, 1935.

8. Elliott, P. C.: Exophthalmic Goiter Before One Year of Age, J. PEDIAT. **6**: 204, 1935.
9. Evans, H. M.: The Growth Hormone of the Anterior Pituitary, J. A. M. A. **104**: 1232, 1935.
10. Gardiner-Hill, H.: Pituitary Disorders in Childhood, Practitioner **134**: 480, 1935; abstract, J. A. M. A. **104**: 2039, 1935.
11. Geiling, E. M. K.: The Posterior Hypophysis, J. A. M. A. **104**: 738, 1935.
12. Hanson, A. M.: Physiology of the Parathyroid, J. A. M. A. **105**: 113, 1935.
13. Hellwig, C. A.: Experimental Goiter: Functional, Chemical and Histologic Studies, Arch. Path. **19**: 364, 1935.
14. Hepler, O. E.: Fat Tolerance in Hyperthyroidism, Arch. Int. Med. **55**: 979, 1935.
15. Hoskins, R. G.: Progress and Problems in Endocrinology, J. A. M. A. **105**: 948, 1935.
16. Loeb, Leo: The Hormones of the Pituitary Gland, Science Supplement **81**: 8, 1935; The Thyroid-Stimulating Hormone of the Anterior Pituitary Gland, Ann. Int. Med. **9**: 13, 1935.
17. Loeb, R. F.: The Adrenal Cortex, J. A. M. A. **104**: 2177, 1935.
18. Loeb, R. F., Atchley, D. W., and Stahl, J.: The Rôle of Sodium in Adrenal Insufficiency, J. A. M. A. **104**: 2149, 1935.
19. Lucchese, G.: Influence of Suprarenals on Formation of Callus, Policlinico **41**: 579, 1934; abstract, J. A. M. A. **104**: 263, 1935.
20. Marine, D.: The Pathogenesis and Prevention of Simple or Endemic Goiter, J. A. M. A. **104**: 2334, 1935.
21. Means, J. H.: Therapeutics of the Thyroid, J. A. M. A. **105**: 24, 1935.
22. Novak, E.: Anterior Pituitary and Anterior Pituitary-Like Substances, J. A. M. A. **104**: 998, 1935.
23. Riddle, O.: The Lactogenic Factor of the Pituitary, J. A. M. A. **104**: 636, 1935.
24. Rose, E., Rose, E. K., and Pendergrass, E. P.: The Treatment of Hyperthyroidism in Children and Younger Adolescents, J. PEDIAT. **7**: 325, 1935.
25. Rowntree, L. G., Clark, J. H., Hanson, A. M., and Steinberg, A.: Biologic Effects of Thymus Extract (Hanson): Accruing Acceleration in Growth and Development in Five Successive Generations of Rats Under Continuous Treatment With Thymus Extract, Arch. Int. Med. **56**: 1, 1935.
26. Rowntree, L. G., Clark, J. H., Steinberg, A., Hanson, A. M., Einhorn, N. H., and Shannon, W. A.: Further Studies on the Thymus and Pineal Glands, Ann. Int. Med. **9**: 359, 1935.
27. Rogoff, J. M.: The Adrenal Medulla, J. A. M. A. **104**: 2088, 1935.
28. Rogoff, J. M.: The Adrenal Cortical Hormone. Experiments With a Commercial Adrenal Extract (Eschatin), J. A. M. A. **103**: 1764, 1934.
29. Saphir, W.: Endocrinology **18**: 625, 1934.
30. Silberstein and Engel: Klin. Wchnschr. **12**: 908, 1933.
31. Smith, P. E.: General Physiology of the Anterior Hypophysis, J. A. M. A. **104**: 548, 1935.
32. Thompson, W. O., Thompson, P. K., Taylor, S. G., and Dickie, L. F. N.: Oral and Duodenal Administration of Single Large Doses of Pure Thyroxine: Comparison of Calorigenic Effects With Those of Monosodium Thyroxine and Thyroxine in Alkaline Solution, Arch. Int. Med. **54**: 818, 1934.
33. Török, G., and Neufeld, L.: Hormone Regulation of Chloride in Children, Monatschr. f. Kinderh. **61**: 73, 1934; abstract, J. A. M. A. **104**: 516, 1935.
34. Turner, H. H.: Diabetes Insipidus: Treatment With Intermedin and Pitmelanin: Preliminary Report of Five Cases, Endocrinology **19**: 275, 1935.
35. Weatherwax, J. L.: Physics of Radiology, New York, 1931, Paul B. Hoeber, p. 107.
36. Webster, B.: Effect of Anterior Pituitary-Like Principle From the Urine of Pregnancy on Undescended Testes in Man, J. A. M. A. **104**: 2157, 1935.
37. Wells, H. G.: Dwarfism Associated With Lingual Goiter and Cystic Hypophysis, Arch. Path. **20**: 64, 1935.

American Academy of Pediatrics

Proceedings

FIFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

NEW YORK CITY, JUNE 7, 1935

Round Table Discussion on Prematurity

The meeting was called to order at 2:00 P.M. in the Hotel Waldorf Astoria, by the chairman, Dr. Julius H. Hess, Chicago, Ill.

A City-Wide Plan for the Reduction of Deaths Associated With and Due to Prematurity

Julius H. Hess, M.D., Chicago

Infant death rates in many large cities have remained at practically the same percentages with relation to the total of births during the past five or more years. In Chicago the deaths per thousand live births (under one year of age) were 1930, 53.4; 1931, 56.4; 1932, 48.2; 1933, 48.8; 1934, 47.7.

A study of the reported causes of death led us to believe that efforts to reduce those death rates further must be directed toward those conditions associated particularly with early infancy, such as birth injuries, premature birth, and congenital malformations. Obstetricians have been directing their attention more recently to a study of comparative results following the institution of the various operative procedures. More recent reports from the Massachusetts General Hospital by Clifford and from Minneapolis by Huenekens emphasize the disadvantages of cesarian section. Further, Clifford and Sisson, in cooperation with their obstetrical staffs, have given much thought to the relationship of the size of the fetus to the chances of survival of the infant and, of equal importance, its relationship to intracranial hemorrhage and other injuries. There still remains much to be accomplished in these fields.

Prematurity was stated as being the cause of death in 749 infants during 1934 in Chicago. A reduction in morbidity and mortality rate among prematurely born infants in our hospitals, therefore, seemingly offered a promising field for lowering the death rate among newborns. It was felt that, if the same principles established in conducting the premature station at Sarah Morris Hospital could be applied in a Chicago-wide program, many premature infants now lost might be saved.

The Sarah Morris Station offers:

1. Ambulance service by the hospital.
2. Premature ward care—with special equipment for oxygen therapy and other types of emergency therapy.
3. Nursing service by a trained personnel.
4. Breast milk obtained from wet-nurses and visiting mothers.

5. Fild nursing service for instruction of the mothers, special attention being given to the promotion of breast milk secretion. Breast milk in the home reduces the number of hospital days.
6. A supply of a simple type of heated beds is lent for the use of graduates in the home. This is of special value in reducing the number of return cases due to acute illnesses after discharge.
7. An out-patient clinic is maintained for instruction of mothers and the care and supervision of graduates not having private physicians.

With the hope of lowering Chicago's newborn infant mortality rate, Dr. Herman N. Bundesen, president of the Board of Health of Chicago, became interested in promoting a city-wide effort to save some of these small infants.

EXHIBIT I

MINIMUM REQUIREMENTS FOR HOSPITAL CARE OF PREMATURE BABIES

TO BE POSTED IN A CONSPICUOUS PLACE IN THE NURSERY

ACCOMMODATIONS—It is recommended that if possible, a separate room be set aside for the care of premature infants. Otherwise they may be cared for in the nursery.

Every hospital should have some type of heated bed in the nursery or premature room.

Oxygen should be used whenever indicated and a supply for use in emergencies with necessary equipment should be kept in the room occupied by the premature infants.

Provision for the prompt transfer of the premature infant from the delivery room to the nursery should be made, so that there is no exposure of the infant to chilling.

EQUIPMENT FOR NURSING CARE—Individual equipment should be provided for the premature infant especially a bath basin and a thermometer.

If the premature infant is cared for in the nursery with the other infants, it is advisable to keep the feeding equipment for stored breast milk (droppers, nipples, etc.) in a separate place from that of the other infants.

Every baby should have his own catheter.

There should be running water in the room or nursery, or it should be easily accessible.

Cans or diaper bags should be available for soiled linen and diapers. If possible, a warmer for clothing and diapers should be available.

The room or nursery should have a "high and low" thermometer (to show the temperature variation within 24 hours) and a hygrometer.

A heated bath table is desirable.

NURSING CARE—The nursing care of the premature infant should be supervised by a graduate nurse, who has had special training in the care of the premature infant. The Board of Health, upon request, will send a nurse to give instructions in the management of premature infants. A twenty-four-hour nursing service should be provided. Nurses and attendants with respiratory or intestinal infections should be excluded from the nursery.

A minimum amount of handling is advised for premature infants. There are few nursing procedures, with the exception of weighing and bathing, which necessitate removal of the infant from the heated bed.

Wool is the preferable material for the clothing of the premature and the infant must, at all times, be guarded against exposure to cold during dressing.

It is recommended that physicians, nurses and all others entering the room in which the premature babies are cared for should wear a clean gown and face mask.

The room temperature should be 78-80°.

Proper nursing hygiene, especially washing of hands, is essential to prevent infections. Infected cases should be isolated.

It is advised that every premature baby receive breast milk. If the milk is obtained outside of the hospital, it should be boiled in the hospital for from one to two minutes before it is used.

The Board of Health, upon request, will furnish information as to where breast milk for premature infants can be obtained.

Nurses caring for premature infants should be familiar with the methods of treating cyanosis in such infants.

It is strongly recommended that the obstetrics department in hospitals where it is customary to place the responsibility for care of the newborn upon the pediatric department, notify the pediatric department in advance of every delivery in which the utero-gestation is expected to be less than term and more than four months. It is also suggested that the pediatric department respond to such notification by assigning to the delivery room and attendant especially trained in the early care of premature infants. Such attendant should be a member of the hospital personnel and constantly on call. The premature infant should always be placed under the care of the premature department immediately after birth.

DISCHARGING INFANTS—No premature infant who will not be under the care of a private physician at home should be discharged from a hospital without first notifying the Board of Health. If parents are not financially able to have a private physician for the infant after its discharge from the hospital, the Board of Health will assign a nurse to the home to give instructions to the mother and to render the necessary follow-up service.

Therefore, we developed the following program, which is an attempt to apply institutional procedures, expanded to meet the demands of a large metropolitan community.

It became apparent that it would be necessary to determine through a survey exactly what facilities the hospitals of Chicago afforded for the proper care of the premature infant. This seemed the more important in that an analysis of the death certificates of the year 1934 showed that the death rate of premature infants in institutions properly equipped for their care was from one-tenth to one-fifth that of the rate in institutions where such care was not available. The percentage of deaths among premature infants who were born and died in the twenty-four hospitals of Chicago having the highest number of regular births were as follows: Three reported less than 10 per cent; three others, less than 20 per cent; eleven, between 20 per cent and 30 per cent; and six, between 30 per cent and 40 per cent and one 70 per cent.

Before making the survey, with the advice and help of the physicians who had specialized in the care of the premature infant, a set of minimum requirements for hospital care of premature infants was drawn up. These requirements served not only as a yardstick for the survey but a copy was sent to every hospital to be posted in a conspicuous place in the nursery (Exhibit I).

Requirements for Hospital Care of Premature Infants.—A graduate nurse, trained at the Sarah Morris Hospital Premature Station and experienced in the care of the premature infant, was assigned to make such a survey. She has been engaged in this service for three months and is now making a resurvey.

After the completion of the survey a scoring sheet was drawn up, and each hospital was rated on the basis of equipment for caring for the premature, as compared with the minimum requirements established by the Board of Health (Exhibit II).

EXHIBIT II—SCORING SHEET

Hospital		
Accommodations		
Room		
Separate	3	
Section of nursery	2	
Incubators		
Grade 1	20	
Grade 2	15	
Oxygen	6	
Delivery room satisfactorily located	1	
Isolation room for infected cases	2	
Equipment		
Individual equipment		
Bath basin	2	
Thermometer	1	
Running water in nursery or workroom	7	
Cans for soiled linen or diaper bags	1	
Hygrometer	1	
Heated bath table	1	
Separate equipment for premature infants	1	
Sterilization process satisfactory	2	
Provision for refrigeration of feedings		
Ice box in nursery	2	
Other ice box	1	
Nursing care		
Graduate nurse in charge of obstetrical division during 24 hours	5	
Satisfactory personnel	3	
Supervision of health of nurses	1	
Gown technic	1	
Face masks	1	
Temperature of nursery or room	1	
Washing of hands	7	
Consulting pediatrician	7	
Satisfactory methods of resuscitation	4	
Breast milk	20	

All hospitals which did not meet these requirements were sent a detailed statement of the points in which they fell short and given a definite period of time

in which to secure the equipment necessary. A follow-up investigation for assistance to the hospital is also made by a specially trained physician.

The survey showed that there were two hospitals, i.e., the Sarah Morris and the Cook County Children's Hospitals, maintaining well-equipped premature stations and receiving infants born outside of their own hospitals. In these two institutions the premature station is completely independent of other hospital departments. Their respective capacities are 25 and 35. Equipment and trained personnel are commensurate with the demands of such a service. It is a part of the general plan to have a third such station opened as soon as possible, preferably in a large Catholic maternity hospital.

An interesting point brought out by the survey was that, while equipment is important, elaborate equipment does not necessarily mean efficient and effective service. More important is an intelligent understanding of the care of the premature infant, especially in respect to such points as the treatment of cyanosis and knowledge of feeding, with an enthusiastic support regulated by much common sense. With all this it is possible to accomplish much in the interest of the premature infant.

For a better understanding of the causes of death of premature infants, a plan for the investigation of the death of every premature infant in the city after Jan. 1, 1935, was instituted. Wherever any evidence of negligence or lack of equipment is found to be a contributing cause of death, such evidence is recorded on the record, kept by the Board of Health, of the physician or hospital responsible for the care of the infant.

It immediately became apparent that in attacking the problem of prematurity, just as in an epidemic the number of cases of contagion must be known, it would be essential to bring to light the number of premature births. Therefore, on March 5, 1935, the Board of Health passed a regulation making premature births immediately reportable by telephone, followed by written confirmation within twenty-four hours. Notification of this ruling was sent to all physicians, midwives, and hospitals.

The public health nurse has demonstrated her value in so many life-saving activities that it was felt she would be an essential factor in the carrying out of this program. However, if she were to render effective service, it would be necessary for her to be well trained in a rather highly specialized and, as a public health activity, new and untried phase of nursing.

Such a program of training was started at once. The nurses of the staff of the Board of Health were assigned in small groups at a time to Sarah Morris Hospital and Cook County Children's Hospital, which were conducting premature stations. As soon as three nurses had finished the training, the city was divided into three districts and one of these nurses assigned to each district. Each nurse is responsible for the premature infants in her district. As other nurses finished their training and as the work grew, additional nurses were assigned to the districts as needed.

The district nurse is responsible for every premature in that district whether the infant is at home or in a hospital. If the baby is in a hospital, the nurse maintains contact with the hospital so that she will know when the baby is to be discharged. A baby in a hospital may reside in a different district. Therefore, the nurse in the district where the baby is hospitalized notifies the nurse of the district where the baby resides when the baby is to be discharged from the hospital. In all hospital cases the nurse goes to the home shortly after the birth and before the baby is discharged, if it is a hospital case, to see that the necessary preparations are made for the proper care of the baby. All such services are rendered through cooperation with the family physician.

All nurses were instructed in the method of hand expression of breast milk, so that they in turn would be able to teach the mothers of premature infants to maintain the supply of breast milk.

It is particularly important that student nurses be made to realize the importance of breast feeding and be trained in manual expression; she should be able to teach the latter. An effort is being made to have superintendents of schools of nursing include in the curriculum an intensive course in breast feeding and manual expression.

It was realized that there will always be infants who cannot have breast milk from their own mothers and that some of these will be prevented from having it from commercial supplies because of economic reasons. To provide for this latter group of infants, a mothers' breast milk station has been established by the Board of Health. This brings the number of breast milk stations in the city to four; there are three in hospitals (two in the hospitals that maintain the premature stations previously mentioned) and a commercial station in another hospital. The first two hospital stations attempt to care primarily for their own needs, having a limited amount only for sale. It has been agreed with the commercial station that it will take any case that can afford to pay something, though below the price ordinarily charged. The Board of Health station is caring for the wholly free cases.

It is important to understand the relationship of the nurse to the private physician in this program. If an infant is under the care of a private physician, the nurse checks with him before taking active charge of the case. The services of the nurse are at the disposal of the physician. At his request she goes into the home to help in such matters as maintaining the supply of breast milk, teaching the mother manual expression, and, if the circumstances of the family so indicate, assisting with the nursing care of the baby.

A group of infant welfare physicians, the members of which are so distributed as to serve all parts of the city, has been especially trained in giving care to sick premature infants. If a feeding problem or illness occurs in the case of a premature infant and it is not possible to have a private physician, one of these physicians is sent to make a special call.

The Board of Health also purchased a number of heated beds for lending to those institutions and homes where other facilities are not available for maintaining the body temperature of premature babies.

There have been established three additional conference clinics for premature infants who have graduated from hospital premature stations and those born and cared for in their own homes—one each on the north, west and south sides of the city. Others will be opened as needed. The nurse in charge of that particular district will also be in charge of the conference on prematurity.

All cases from the Cook County Hospital needing antisyphilitic care are reported to the Board of Health and then are assigned to the field nurses for special follow-up. This is to insure as nearly as possible the return of these women to the clinics for antisyphilitic treatment.

An illustrated pamphlet, outlining in detail the proper care of premature babies, has been prepared in easily understandable language, and will be sent to all physicians and nurses, as well as the mothers of premature babies.

A study of the death certificates also revealed that many of the premature infants died within several hours of birth. It was thought that possibly in some cases these deaths were the result of improper methods of resuscitation. In order to determine what the medical profession considered acceptable methods, a questionnaire was sent to all physicians practicing obstetrics. The replies to these questionnaires were tabulated. Some methods were found to be in disrepute, while others

were highly advocated. Steps are now being taken to disseminate this information to physicians and hospitals in order to set up a routine for proper resuscitation of asphyxiated infants.

In this campaign there is no great effort put forth in trying to determine new procedures for saving premature babies, but rather the attempt is to secure widespread application of those methods which have been shown to be so successful at the Sarah Morris and Cook County Hospitals premature stations. The program has been under way too short a time to draw conclusions as to ultimate results from this campaign in behalf of prematurely born and congenitally debilitated infants.

As the training of the nurses continues, as hospitals become better and better equipped, and as physicians in hospitals give their attention to the problem, it is believed there will be a steady decrease in the mortality from prematurity. Plans for the future will entail a vigorous attack on the prevention of prematurity through proper and more adequate prenatal care. As previously stated, this phase of the problem is receiving widespread attention throughout the United States, manifestly through cooperation between obstetricians and pediatricians.

DR. ETHEL DUNHAM (NEW HAVEN, CONN.).—I am very much interested in the program which is being carried on in Chicago to cope with the problem of death of premature infants. I have said on many occasions, that we are not all really aware of what a problem it is. The reduction of mortality from prematurity is of the utmost importance in the reduction of the high rate of neonatal mortality. Prematurity ranks by far the highest among the causes of death in infants in the neonatal period.

It is obviously the most important cause of infant mortality, and a very high percentage of all the deaths from this cause take place in the first month. Although in the twelve years from 1921 to 1933 in infants under one month deaths resulting from prematurity in the United States birth registration area are reported to have decreased in number from 27,932 to 19,718, the rate per 1,000 live births in the area decreased only from 16.8 to 15.3 in this comparatively long period of time.

In the different states in the same year, 1933, the mortality rate from reported premature births varied between a low rate of 10.6 reported in Arkansas and a high one of 24.3 in the District of Columbia.

The incidence of premature births for the birth registration area is not known. The figures for New York state have, however, been made available for 1933. There were 3,203 premature births which constituted 3.9 per cent of the total live births in the state for that year. A total of 1,350 deaths from premature birth occurred, a mortality rate 410.8 per 1,000 live premature births. Forty-one per cent of the premature infants born alive died of "premature birth."

Figures on the incidence of premature births in hospitals show considerable variation. Brandt reported an incidence of 10.4 per cent of 5,439 births in Cologne, Germany; Hadley, 6 per cent of 3,079 births in the New Haven Hospital; Clifford, 3 per cent in the Boston Lying-In Hospital.

Reports from hospitals of mortality from prematurity also differ widely. The differences may be attributed in part to variability in criteria for the diagnosis of prematurity, in part to differences in the periods of observation at the end of which the report is made, and in part to the numbers of infants in high or low weight groups.

For example, Clifford reports as premature only those infants who weigh five pounds or less at birth, while Hadley used the criteria established by Ylppo, namely, a birth weight of 2,500 gm. or less. Other observers base the diagnosis on other criteria such as history of period of gestation, clinical evidences, or length, etc. As far as the period of observation is concerned, it is obvious that the same periods as well as the same criteria for diagnosis must be used by different observers to make results comparable.

Ylppo reported that of 668 premature infants studied, 9 per cent died on the first day; 18 per cent before the fifth day; 31 per cent during the first month; 41 per cent during the first six months; 50 per cent during the first year. From the first to the fourth year, however, only 3 per cent more had died. Obviously reports of mortality at the end of the first month cannot be compared with those at the end of six months.

That the mortality of premature infants varies greatly with differences in the birth weights was also pointed out by Ylppo. Though the average mortality during the first month of the total group of 668 infants reported by him was 31 per cent, in the group with the highest birth weight it was 15 per cent; in the lowest it was 84 per cent.

Reports of mortality from prematurity are not very numerous. The total mortality reported varies between 12.9 and 75.5 per cent. It is obvious that it is difficult to evaluate figures of mortality from prematurity for some of the reasons which have been already pointed out.

A study was undertaken in the New Haven Hospital to determine the mortality from premature birth and to set up certain criteria for analysis of material in an attempt to stimulate interest in the problem and to help make results comparable with those of other investigators. The study included 244 liveborn premature infants. All infants were considered premature who lived for any period at all, no matter how short the period, even if the beating of the heart was the only evidence of life. A birth weight of 2,500 gm. or 5 pounds eight ounces or less was the criteria used for diagnosis. All of the infants were born in the New Haven Hospital or cared for in the New Haven Hospital.

The period of observation, from birth to discharge, averaged about forty days. The slide shows the number of infants in each weight group. Sixty-six of the 244 infants died, a mortality of 27.1 per cent. If the mortality in the two weight groups shown on the slide is considered, it was 12.5 per cent for those in the higher weight group but 71.7 per cent in the lower, or more than five times higher in the latter than in the former.

The cause of death of the infants was analyzed. Prematurity alone was by far the most frequent cause and was naturally diagnosed most often in infants of low birth weight. Infection took second place, intracranial hemorrhage third, while congenital defects took fourth place.

The causes of premature birth were studied, and the incidence of complications of the mother's pregnancy was found to be high. The type of complication appeared to be not so important as the time at which the complication occurred; in other words, the weight of the infant was the determining factor in the survival. The conclusions reached were that to reduce mortality from prematurity two lines of attack are clear: first, the prevention of complications of pregnancy which bring about labor so prematurely that infants with a birth weight below 1,500 gm. are born and, second, improvement in methods of caring for these very small infants. Satisfactory reduction in mortality has been made over a period of years among the infants in the higher weight groups, while that in the lower has remained practically unchanged.

CHAIRMAN HESS.—Did you include in your statistics all babies who breathe?

DR. DUNHAM.—Yes.

The Collection of Breast Milk for the Premature Infant

M. L. Blatt, M.D., Chicago

In an effort to decrease the mortality rate in the premature infant ward at Cook County Hospital, the production of a large quantity of breast milk became necessary. The number of premature infants in the ward varies between 20 and 45.

At the beginning of the study four years ago, the only source of supply was the obstetric wards of our own institution. There are 250 births in these wards per month, and the normal mother without complications is discharged from the hospital in from eight to ten days. The milk from these postpartum women was needed for the weak infant on the obstetric service as well as for the premature infant in the pediatric hospital. An irregular supply of milk, rarely exceeding two quarts per day, was available for the use of the premature station. This was obtained with difficulty although a nurse whose special duty was the manual expression of the breasts of these new mothers was put on duty for this purpose alone.

To supplement this inadequate supply, the Women's and Children's Hospital of Chicago furnished us with a limited amount of breast milk at first gratis but later, as their funds diminished, at a cost of ten cents per ounce.

In order that the premature infants' and the children's wards might become independent of the uncertain supply from the obstetric wards and the expensive supplement from the Women's and Children's Hospital, it seemed advisable to establish a breast milk collecting station of our own. Mothers were selected from the obstetric wards to be employed as wet-nurses. It was found impractical to house them. We, therefore, established the price of five cents per ounce for mother's milk; the women were to come into our station twice daily for manual expression. In addition to the cash compensation, these women were given lunch and a quart of milk to drink. The compensation was later reduced to four cents per ounce as we acquired a larger milk supply.

Every mother, before acceptance of her milk, is given a complete physical examination. A history of syphilis or a positive Wassermann reaction, a history of tuberculosis or any tuberculous findings, a positive neiserian slide or evidence of disease in the throat or breasts is sufficient to prevent her acceptance into the group. We place 16 ounces as a minimum production per day for employment. It is found much easier to handle fewer mothers with a large individual milk supply than numerous mothers with a small supply. The time spent in sterilization of breasts, gowns, and necessary equipment is too great to warrant continuing such mothers in the group.

There has been one exception to this rule—in order that the breast milk of the mother whose infant is in the hospital may be continued, she is urged to come to the station for manual expression while her baby is under our care. She receives no compensation for the milk so expressed other than lunch and her quart of cow's milk. By this means we gain a limited amount of breast milk per day and at the same time stimulate lactation in the mothers thus enabling them to take their premature infants home at an earlier age.

Through the cooperation of Dr. Bundesen of the Chicago Department of Health, under Dr. H. C. Niblack's supervision, we have recently advanced this process one step further. Nurses from the department came to us for training in manual expression and care of the premature infant, returning to their district to teach mothers whose infants are in the hospital or at home, too weak to nurse, the procedure of manual expression.

In order to have an adequate milk supply available at all times not interrupted by bad weather or sudden loss of a large number of wet-nurses, it is deemed advisable to collect and preserve such milk as can be obtained beyond our daily need. At Johns Hopkins Hospital, it has been found that boiling the milk in a Mason jar and immediately sealing it (cold pack) are adequate for preservation. We instituted the same method and have kept milk for as long as ninety days without apparent deterioration. The milk becomes brown with such boiling, and when iced the fat separates in a hard mass. Bacteriologic examination shows it to remain sterile. Occasionally a few hay bacillus are reported by the bacteriologist, but at no time

have we had difficulty from feeding this product. We make an effort to keep on hand at least 30 quarts of such milk. We are at present fractionally sterilizing by ten-minute boiling on three successive days in place of the single sterilization. The supply is only a few weeks old. It is used to complement feedings for the weaker infants, not premature infants in our own and other wards. When necessary, it has been fed to premature infants, who have done well with it.

It has long been a point of observation that breast-fed infants thrive and have a better tissue turgor than do those artificially fed. We decided, therefore, to produce a raw breast milk which could be preserved in its natural state and fed to the premature infant, using an aseptic technic and rapid cooling in the milk laboratory. We have produced and are feeding such a milk.

In order to produce a maternal milk with as low a bacterial count as possible, the wet-nurse removes her street clothing and dons a hospital gown, cap and mask. She then scrubs her hands and nails. Then she puts on a short rubber apron below the breasts, and a trained nurse cleanses her breasts with soap and water. The wet-nurse then cleanses her own breasts with boric solution. Her hospital gown is removed, and she is assisted by a trained nurse in putting on a sterile gown with separate breast curtains.

She steps into the milk collecting room where her milk is collected in a sterile graduate and poured into a graduated nursing bottle. Some of the women prefer a hand breast pump to start the milk flow. Manual expression is employed, and the milk collected in the sterile graduate (others use an Abt pump or hand breast pump).

After the milk is collected in the graduate, the wet-nurse pours it into the nursing bottle. Bottles are labeled, and the milk is iced immediately. It then goes to the milk laboratory where it is pooled in a sterile coffeepot to be poured into Kelley flasks. Surgically clean nurses prepare the formulas, transferring the milk from these flasks into graduated cylinders, if a compound formula, and directly into nursing bottles, if a simple one.

Breast milk consumption at the Cook County Hospital has steadily increased from 24,126 ounces in 1931 to 97,399 ounces in 1934. During this time, the amount of milk accepted from outside sources has been gradually reduced, and in 1934 all breast milk consumed was produced in the hospital under surveillance of a trained staff.

During 1934, 61,574 ounces were collected from wet-nurses in the breast milk station of the Cook County Hospital; 25,667 ounces were collected by a trained nurse in the obstetrical department, and an additional 10,157 ounces were collected in the breast milk station from mothers of infants in the hospital.

CHAIRMAN HESS.—What was the cost of breast milk at the County Hospital preceding the opening of our own station?

DR. BLATT.—In 1932 our costs were around seven or eight cents an ounce. When we reached the peak, that is ninety-seven thousand ounces, we were paying only four cents an ounce for the production, and our cost per month never was over two hundred dollars. The establishment of the station has produced an *esprit de corps* between general ward nurses, dietitians, and premature station nurses which we have never had before. They take great pride in this work, and, if we have accomplished nothing more, the work of Dr. Bundesen and Dr. Hess has made the practitoners, resident and interne, the nurses, and certainly all the pediatricians more "premature conscious" than before.

DR. STEWART CLIFFORD (BOSTON) referred readers to his paper in the round table discussion of last year. (J. PEDIAT. Vol. 6, p. 115, 1935.)

DR. L. EMMETT HOLT, JR. (BALTIMORE).—I would like to ask Dr. Clifford how the reduction of stillbirths in the Boston City Hospital was brought about. Nor is it

clear to me how the pregnancy was prolonged in order to make these premature infants more viable.

DR. CLIFFORD.—The stillbirths were reduced principally in the toxemic group; about 30 per cent of our premature infants born alive are from mothers with toxemia. A larger per cent of the premature infants born dead came from mothers with toxemia (according to the Bodes differential diagnosis of toxemia, that is, a mother who has a blood pressure of 140 without albumin). We shall not go into the controversial subject of the diagnosis and classification of toxemia; using the progressive differential diagnosis, we have diagnosed as toxemic 12 per cent of the women who appear in the clinic for prenatal studies. Of the 12 per cent, 6 per cent deliver stillborn babies. One-half of these weigh more than five pounds and half less than five pounds.

The obstetric management of these patients now is such that when the patient appears with a toxemia of moderately severe degree, an appraisal is made of the size of the baby and of the type and the degree of toxemia. We found in women whose blood pressures went to 180 or above, 50 per cent of those with a severe grade of toxemia delivered stillborn babies. The case is considered first, from the standpoint of the mother's condition and second with regard to the chances the baby will run as a premature infant or one of the weight it is shown to be by x-ray pictures.

If we find that by x-ray examination a mother has a 4-pound baby, that she has a blood pressure about 180, and that she has lost one or more babies by miscarriage, the conclusion may be reached that the mother delivered of her 4-pound baby will have a greater chance of having a baby to take home with her than she would if we waited for a larger sized baby only to have it delivered stillborn. It is largely from the toxemic patients that the stillborn infants are salvaged.

Cases of placenta previa make up the other group. If bleeding is taking place, the fetus undergoes marked intrauterine asphyxia. The danger of the baby's being born dead increases from the onset of bleeding to the time when the baby is actually delivered. Women with placenta previa should not be examined and bleeding started, if there is just a slight flowing, until the baby is demonstrated to be of sufficient size to be viable; and then if necessary a cesarean section should be performed.

DR. HOLT.—The second question concerns the circumstances under which you prolong pregnancy to make the child more viable.

DR. CLIFFORD.—In the milder cases of toxemia, if the mother has about 160 blood pressure, a slight trace of albumin, a baby shown by x-ray to approximate, let us say only 3 pounds, the mother is put to bed in the hospital under close observation and kept there for two or three weeks. Under these well-controlled conditions in borderline toxemic cases, you can often prolong pregnancy and, instead of delivering at 3 pounds, deliver the infant at 4 or 5 pounds. The obstetrician has to determine the size of the baby, the blood pressure, and other findings of the mother.

DR. BLATT.—You have not described what to do for a mother who comes to the institution in early labor.

DR. CLIFFORD.—You cannot do anything.

DR. BLATT.—That is why we think our statistics are very high. The interne or resident obstetrician says the pregnancy will be aborted unless the woman is given morphine. Then she delivers a premature baby, and we are charged with a premature death.

DR. CLIFFORD.—The staff has given considerable study to the effect of avertin and found it could be used effectively instead of morphine or ether to stop labor. Under certain conditions one may be forced to give morphine. The mother comes first.

DR. BLATT.—When avertin has been used, the babies seem very dull for about forty-eight hours.

DR. CLIFFORD.—Any analgesic given to the mother affects the baby to some degree. Dr. Irving had a very interesting experiment. He took five hundred consecutive deliveries in the district where no anesthesia was used. Only 10 per cent of the babies required resuscitation. He compared the series receiving so-called twilight sleep analgesia, and, instead of 10 per cent requiring resuscitation, 60 per cent had to be resuscitated. He compared that with the analgesia now popular—phenobarbital. There 40 per cent had to be resuscitated, fewer than in the morphine group, but still many more than in the group without anesthesia.

That is the price we pay for analgesia. If you take a 7- or 8-pound baby and put him to sleep with analgesia, what are you going to do with a 3-pound baby? Those are the babies who are being born dead. They do not enter into any of our statistical figures. Every one washes his hands of a stillborn, and nobody assumes responsibility.

Through this study we are making on premature infants, we are all going to end by including stillborns. We will have to include them in our group. There is no reason why a baby at ten o'clock is stillborn but at ten-two premature.

DR. HUGH CHAPLIN (NEW YORK CITY).—Do I understand that the premature infants born alive did not show any serious after-effect in connection with toxemia?

DR. CLIFFORD.—The toxemia does not apparently affect any infant directly. A mother may have a high N.P.N. level with toxemia and may be really in convulsions, but the infant may have a normal N.P.N. content. If that toxemia produces premature separation of the placenta, the baby is killed by interruption of the placental circulation. As a whole, the babies of toxemic mothers are less well nourished than the babies of normal mothers. The babies of toxemic mothers constantly approach the minimum weight for their size.

CHAIRMAN HESS.—Dr. Clifford has brought up the question of resuscitation of infants. Believing that some of the methods used for resuscitation of premature infants traumatize them, the Commissioner of Health of Chicago sent out a questionnaire to the obstetricians of Chicago, asking for their opinions as to the methods which might be advisable and safe for the newborn. The conclusions were that posture, pharyngeal, and, in exceptional cases, tracheal aspiration, oxygen, oxygen and carbon dioxide mixtures, warm baths, and mild forms of artificial respiration were recommended. All strenuous handling which might traumatize the infant was condemned.

Dr. Huenekens has recently stated that the tying of the cord of prematurely born infants almost immediately might be a factor in the high mortality rate.

DR. EARLE.—You spoke of breech delivery and cesarean section being equally dangerous. May I ask whether any of the mothers are allowed to have a trial by labor on the basis of measurements before cesarean section is performed?

DR. CLIFFORD.—Unless there is a necessity of early induced labor. The mother may have heart disease with impending failure or may have severe pre-eclampsia. The cesarean section is performed not because of any question of disproportion and not for the baby, but for the mother.

DR. LEWIS A. KOCH (Brooklyn, N. Y.).—I should like to present a summary of a statistical study of the incidence of prematurity and its etiology and mortality as it occurred at the Long Island College Hospital during a ten-year period from Jan. 1, 1924 to Jan. 1, 1934. There is a well-organized prenatal clinic which assigns most normal cases to the student out-patient service for home delivery. Toxemia cases are managed in a very conservative manner and an attempt is made to prolong the pregnancy until term; very few inductions are practiced. The question arises in the light of Dr. Clifford's interesting work whether the relative incidence of stillbirths is appreciably higher as a result of this conservative attitude.

In this study, all infants, whether of single or multiple pregnancy, who were born alive (heart beating) and whose weight at birth was 2,500 gm. (5 pounds 8 ounces) or less were considered as premature, regardless of the period of gestation. It is routine for all infants born in the hospital to be placed in a heated bed in the delivery room immediately after birth, and as a result initial chilling seldom occurs.

Following delivery, the infants are transferred immediately to the pediatric service for the remainder of their care. Air-conditioned rooms are not available, and individual incubator care has to suffice. The nursing care is done chiefly by student nurses with a minimum number of graduate nurses in charge. The pediatric care varies but in few details from that practiced in other teaching institutions with which I am familiar. Probably human milk has been more available at this institution than at most since a human milk collection depot was maintained by the Children's Welfare Federation in the out-patient department for many years.

During this ten-year period, 8,345 mothers were delivered in the Long Island College Hospital; 553, or 6.6 per cent, were delivered of living premature infants.

The average premature mortality was 30.5 per cent.

The incidence of prematurity among mothers who had had previous early labors was three and one-half times higher than the average total incidence of prematurity.

Multiple pregnancies occurred 95 times, of which infants 46.8 per cent were considered and treated as premature.

In one-half of the cases, no cause for early labor was apparent. In one-fifth of the cases, toxemia of pregnancy was considered responsible for the early labors; syphilis in this series was a relatively minor cause (4.5 per cent).

The mortality among those infants born of mothers suffering from toxemia was no greater than those of mothers with no apparent cause for their early labors.

Premature infants whose mothers suffered from heart disease, acute febrile diseases, placenta previa, and syphilis were apparently less viable than those with no apparent cause for their early labors.

The mortality among infants weighing less than 2,500 gm. who were born of multiple pregnancies was as high as among those of single pregnancies.

The type of labor apparently had but little influence upon the mortality rate of the premature infants. However, the type of delivery seemed of definite importance. The infant mortality in this series was definitely higher among the breech delivery cases than among the spontaneous vertex, forceps, and cesarean section cases. The mortality among those born by cesarean section was slightly less (27.4 per cent) than the total average mortality (30.5 per cent).

There was a definite decrease in the mortality of premature infants during the last two years of this study. This is attributed to the increase in the number of graduate nurses in attendance.

Over half (57.7 per cent) of the premature infant deaths occurred during the first forty-eight hours of life. The discoverable causes of death among this group were asphyxia, persistent atelectasis, and intracranial hemorrhage. Among those surviving the first forty-eight hours, acute infections, especially bronchopneumonia, were the most important causes of death.

Toxemia occurred as a complication of pregnancy in approximately 8 per cent of the cases admitted to the obstetric service. In less than 6 per cent of these toxic cases was cesarean section performed or labor induced by bougie or bag. In 75 per cent, labor was spontaneous resulting in living babies weighing more than 2,000 gm. (average 2,950).

There were but 36 among 661 cases of toxemia which resulted in stillbirths weighing more than 2,000 grams and whose hearts were not heard at the end of the first stage of the labor. These infants might have been born alive if labor had been induced earlier. However, since many of the intrauterine deaths in toxemia occurred in cases in which the blood pressure was not alarmingly high, and since the great majority were carried to term with conservative treatment, it might be unwise to recommend early induction of labor as a routine in all cases.

CHAIRMAN HESS.—One point which might account for the gross number in Dr. Koch's series as compared with Dr. Clifford's is the fact that Dr. Clifford has his dividing line at 5 pounds and Dr. Koch has his dividing line at 5.5 pounds.

DR. CLIFFORD.—It is a most instructive paper, and it is very interesting to find many points of similarity in the statistics from the two institutions. By comparison of statistics such as we have heard, we shall know our sore points and can reappraise our methods to see whether we cannot approach the Long Island figures in certain respects, particularly toxemia.

In toxemia a placenta can be severely infarcted. Very frequently you will find a clot that may possibly account for the intrauterine death between the first stage and termination. The placenta, microscopically and grossly, is a very much diseased organ.

DR. DUNHAM.—My plea has always been for collecting figures and analyzing the figures, but I do think we have to be very careful in the interpretation of them. I was reminded of this when Dr. Koch spoke of the comparison of mortality rates between twins and single births, because I had analyzed our twin and single births and thought the mortality among the twin births was lower until I had interpreted the figures and found no significant difference in them. I think we should be careful about having four cases and saying 50 per cent die, comparing those with one hundred cases in which twenty-five die. You cannot make comparisons of that kind on a statistical basis.

One of the things in which we are most interseted in all this work on prematurity is to get large enough figures so that they will be significant statistically. One reason why we are so anxious to have every one working on the same criterion is so we can really pool figures.

CHAIRMAN HESS.—You are suggesting the use of what figures as the dividing line?

DR. DUNHAM.—We have urged the use of 5 pounds 8 ounces because Ylppo laid down that line back in 1919. The 2,500 gm. weight is one that every one could use. If we can all agree on a weight to use in the analysis of our figures, it will be much easier to compare notes.

DR. CLIFFORD.—As a result of Dr. Dunham's work and in order to make our figures available, we are now keeping our figures at 5½ pounds. I have only one plea to make, which is that, instead of taking from 0 to 5½ pounds as Dr. Dunham recommends, we subdivide our figures into some unit or series of units. I would suggest 500 gm. weight groups.

The following resolution was passed:

For statistical purposes and comparison of results of care, a uniform standard for diagnosis of prematurity is important.

A premature infant is one who weighs 2,500 gm. or less at birth (not at admission) regardless of the period of gestation.

All liveborn premature infants should be included, evidence of life being heart beating or breathing.

Mortality should also be calculated:

1. In weight groups: number of cases should be studied in five weight groups—
   (1) Under 1,000 gm.
   (2) 1,000-1,250 gm.
   (3) 1,251-1,500 gm.
   (4) 1,501-2,000 gm.
   (5) 2,001-2,500 gm.
2. Age at time of death of various weight groups.
3. Age at time of admission of infants received from other hospitals and homes in relation to Sections 1 and 2.

DR. EDWARD A. WAGNER (CINCINNATI, OHIO) presented the following figures on the mortality in relation to estimated fetal age and weight in 113 premature infants:

ESTIMATED FETAL AGE	WEIGHT	NO.	MORTALITY	PERCENTAGE
4 mo.	1-10-10½	2	2	100
5 mo.	1-12¼	2	2	100
6 mo.	19-3.2	14	12	85
7 mo.	2.4-5.9¾	43	29	67.4
8 mo.	3.7-4.15	45	17	37.7
9 mo.	3.14-4.14	7	2	28.5

The causes of death as ascertained in twenty-eight autopsies were as follows:

Intracranial hemorrhage	15	14%
Enteritis	4	14%
Cerebral congestion and edema	3	
Lobar pneumonia	5	8%
Hemorrhage—hematoperitoneum	1	

DR. WALTER F. WATTON (BROOKLYN, N. Y.).—The number of births at the Brooklyn Methodist Hospital during the five-year period beginning 1930 and ending 1934, inclusive, was 9,224. Among these there were 564 premature births, making 6 per cent of the total number. This group includes all premature babies who showed any signs of life on delivery, irrespective of the months of gestation. We have not classified as premature that large group of small babies weighing less than 2,500 gm. with an obstetric history of being carried more than 8½ months.

TABLE I

Number of premature infants for the 5-year period from 1930 to 1934, inclusive	564	
Number of premature infants who lived	417	74%
Number of premature infants who died	147	26%
Number of premature infants weighing more than 2,500 gm.	214	
Number of premature infants weighing 2,500 gm. or less	350	
Number of deaths of premature infants weighing more than 2,500 gm.	21	OF TOTAL 14%
Number of deaths of premature infants weighing 2,500 gm. or less	126	86%
Mortality rate (omitting all premature infants over 2,500 gm.)		36%

There were 417, or 74 per cent, of these premature infants who lived, and 147 babies, or 26 per cent, died (Table I).

In our total group of premature infants there were 214 with birth weights above 2,500 gm. and 350 with birth weights of 2,500 gm. or less. Of the 147 deaths only 21, or 14 per cent, weighed more than 2,500 gm., while 126, or 86 per cent, of the total deaths fell in the lower weight group (Table II).

TABLE II

DEATHS

Total number of deaths	147	
Lived less than 1 hour	36	
Lived less than 1 day	49	
Lived less than 2 days but more than 1 day	9	
Lived less than 1 week but more than 2 days	13	
Lived more than 1 week	40	
Deaths before end of second day (obstetric problems)	94	
Deaths of premature infants 2 days or older (pediatric problems)	53	DEATH RATE 11.2 per cent

The period of gestation is the most important factor of the premature problem. Babies of less than six and one-half months' gestation practically all die (Table III). Since these babies were listed as premature, we have had to include them in this report. Of the infants born in the eight and one-half months' period, we lost only 3 per cent.

TABLE III

PERIOD OF GESTATION

PERIOD OF GESTATION (IN MO.)	NUMBER OF BABIES	NUMBER OF BABIES WHO LIVED	NUMBER OF DEATHS	PERCENTAGE OF DEATHS
4	1	–	1	100
4½	2	–	2	100
5	3	–	3	100
6	31	2	29	93
6½	16	3	13	87
7	74	41	33	45
7½	44	28	16	36
8	277	231	46	16
8½	116	112	4	3

A record of the feedings of these babies showed that 65 per cent of them received breast milk exclusively or part breast milk and that 35 per cent received artificial food only (Table IV). We could not classify fairly the results from artificial feeding and breast milk feeding because our weaker smaller babies obviously, having the less chance of survival, were given breast milk. There were seventy-one babies in this group who did not live sufficiently long to receive any feedings.

In reviewing the causes of the pediatric deaths of this group aside from prematurity alone, the problem of infection plays a very major part. Infections in premature infants seem to select the gastrointestinal and respiratory tracts most frequently. Some of the other more frequent causes of death among the premature infants were congenital malformations, intracranial hemorrhages, congenital atelectasis, asphyxia neonatorum, hemorrhagic disease of the newborn, and syphilis (Table V).

TABLE IV

FEEDINGS

	NUMBER OF BABIES	PERCENTAGE	
Breast milk only by nursing the mother	30	6.0	
Breast milk pumped, and also nursing mother	9	1.8	
Nursing and a whole milk formula P.C.	36	7.3	
Nursing and an evaporated milk formula P.C.	58	11.8	
Pumped breast milk only	54	11.0	
Pumped breast milk and whole milk formula	25	5.5	
Pumped breast milk and evaporated milk formula	106	22.0	65
No breast milk—evaporated milk formula only	142	28.8	
No breast milk—whole milk formula only	29	5.8	
No breast milk—evaporated milk and whole milk formula	4	0.8	35
Babies who did not live long enough to receive any formula	71		
Total	564		

TABLE V

PREDOMINATING CAUSES OF DEATH

Prematurity alone	61
Prematurity with gastroenteritis	16
Prematurity with bronchopneumonia	15
Prematurity with gastroenteritis and bronchopneumonia	14
Prematurity with congenital malformations	11
Prematurity with intracranial hemorrhage	11
Prematurity with congenital atelectasis	9
Prematurity with asphyxia neonatorum	4
Prematurity with hemorrhagic disease of newborn	3
Prematurity with syphilis	2

After tabulating the various maternal diagnoses in the premature group, we note that toxemia was most common. Hemorrhages, including placenta previa, ablatio, etc., hold an important place in maternal diagnosis (Table VI). There were a few cesarean births, especially among the toxic mothers; however, this represents only 24 out of the 302 cesareans performed during this period. Syphilis in this group seems to be of minor importance as one of the causes of prematurity because we have a class of patients in whom the incidence of syphilis is unusually low.

TABLE VI

MATERNAL DIAGNOSIS IN PREMATURE GROUPS

Toxemia (including chronic nephritis)	120
Multiple pregnancies	49
Hemorrhages (placenta previa, ablatio, etc.)	38
Cesarean births	24
Cardiac disease	10
Hydramnios	10
Fibroids	9
Premature rupture of membranes	8
Pyelitis	8
Syphilis	8

Every premature infant who breathed is included in this series. The general mortality rate of our premature infants was 26 per cent. If all premature infants weighing over 2,500 gm. are omitted, the mortality rate was 36 per cent; and if the premature infants classified as obstetric problems because they lived less than two days are omitted, the pediatric mortality rate was then 11.2 per cent. We find that infections still play altogether too great a rôle in the causing of premature deaths; that 65 per cent of all of these premature infants were fed in part or totally on breast milk, which we believe is ideal; and that 35 per cent had to rely on a formula only. This study emphasizes that toxemia, multiple pregnancies, and hemorrhages stand high as important causative factors of prematurity.

CHAIRMAN HESS.—We have a very progressive commissioner of health in Chicago who believes that premature infants should be taken care of by a pediatrician. His recommendation was as follows: It is strongly recommended that the obstetric departments in hospitals where it is customary to place the responsibility for the care of the newborn upon the pediatric department notify the pediatric department in advance of a delivery in which the uterogestation is expected to be less than term and more than four months. It is also suggested that the pediatric department respond to such notification by assigning to the delivery room an attendant, especially trained in the early care of premature infants. Such an attendant should be a member of the hospital personnel and constantly on call.

DR. CHAPLIN.—To what extent does humidity play a part in this matter of mortality?

CHAIRMAN HESS.—There is a good deal of diversified opinion. When I discussed the requirement for a station in a small hospital, the opinion was expressed that that equipment was of less importance than good nursing care and breast milk. We have no provision for controlling humidity other than opening windows or hanging wet sheets over an ordinary screen.

We believe our results, both as to morbidity and mortality, compare favorably with any results so far published. I think Dr. Dunham might want to say something on this subject. The system at Yale has been modified like that at Harvard to control ventilation, humidity, and temperature.

DR. DUNHAM.—We have analyzed all the cases in the last eight years from the viewpoint of how the treatment affects mortality. During the last four years we have had air-conditioned rooms. During the previous four years, we had no air-conditioned rooms. It is not a satisfactory comparison because the cases were not in all other respects the same.

We found, in comparing the mortality in the two four-year periods, that we lowered the mortality in the higher weight groups, those over 1,500 gm., but had not affected the mortality in the lower weight group. Since one would expect and hope that an air-conditioned room would be a great asset to the babies in the lower weight group, we do not feel we have anything definite to show.

CHAIRMAN HESS.—How about the morbidity?

DR. DUNHAM.—I cannot give the results, but they are not very striking.

DR. EGBERT EARL MOODY (Los Angeles).—We have heard all the figures from the East. We will give some figures from Los Angeles. Since January, 1934, I have had charge of the newborn service at the Los Angeles General Hospital. We have as our premature nursery an ordinary nursery. We have no graduation room, no apparatus for humidity. Our sterilizer was put into the room for sterilization. That has been largely the method by which our humidity has been controlled. In our heat bed we use only a pan of water.

Since January, 1934, we have admitted to this department for premature infants only those who are born in the hospital, or infants born outside whose mothers come into the hospital bringing their infants with them. We accept no premature infants except those accompanying the mother to the obstetric ward.

We have had during the seventeen months, and these figures are up to May 25, 1935, 429 premature infants of whom 311 lived. Of the group under 3 pounds, only 9 lived, a mortality of 90 per cent. In the weight group between 3 and 4 pounds, 58 children lived, a mortality rate of 30 per cent. In the weight group between 4 and 5 pounds, we had 109 children with a mortality rate of 8 per cent. Between 5 and 5½ pounds, 135 infants lived, a mortality rate of 4 per cent. We obtained autopsies in 59 per cent of the deaths. It was interesting to note that atelectasis was indicated in 50 per cent of these cases. Cerebral hemorrhage accounted for death in 15 per cent, pneumonia 7 per cent, syphilis, and otitis media each 4.5 per cent.

It is interesting to note that enteric infections were almost nonexistent. These babies were fed exclusively, up to 4 pounds in weight, with breast milk. During this time, our service has used more than 50,000 ounces of breast milk, which has been furnished by a wet-nursing bureau run in connection with one of the smaller clinics as a commercial enterprise.

Seventy-five per cent of the deaths occurred before forty-eight hours elapsed. Eighty-one per cent of these died within twenty-four hours. We considered as premature any infant who reached the premature nursery. There has not been good liaison between the obstetric and the pediatric departments; consequently, those babies who died before they reached the premature room are not included in the record.

DR. J. VICTOR GREENEBAUM (CINCINNATI).—In the Jewish Hospital, we installed six of Dr. Hess' beds and reduced our mortality to less than 20 per cent for the babies born in the hospital. For the children who are brought into the hospital, the statistics are less favorable.

DR. C. W. WYCKOFF (CLEVELAND).—What is your experience and the experience of other men in the follow-up work on premature infants six months and twelve months after birth, as to paralysis, hydrocephalus and so forth?

CHAIRMAN HESS.—Moore and Bartelme selected for a mental and physical study the 250 oldest premature infants discharged from our station. The station has now been open thirteen years. Among the 250 are all of the cases of intracranial hemorrhage which we could locate. There was a total number of 69 cases which were diagnosed as intracranial hemorrhage while in the hospital or in which evidence of hemorrhage appeared after graduation. Of those 69, 42 show no physical or mental defect. Eleven are in what we call a "bad" group, of which either 6 or 7 are mentally deficient and the other 4 or 5 are physically subnormal. The next group, those showing moderate evidence, includes 9, and of those 4 are mentally deficient. Five are fairly good mentally but show more or less what I would say was at least moderate physical change. Of the 7 in the other group, 2 are mentally deficient, and the other 5 show very minor evidence of hemorrhage. Two of them are moderately retarded, and 5 show such minor changes as strabismus, increased reflexes, and so forth. Twenty-seven out of 69 show more or less severe changes; 42 none, so far as we could find, mentally or physically. Undoubtedly we have lost sight of a considerable number. Some of them died.

We have had up to Jan. 1, 1934, 168 cases showing intracranial hemorrhage out of 386 which we autopsied.

The meeting adjourned at 5:30 P.M.

MEETING OF THE EXECUTIVE BOARD OF THE AMERICAN ACADEMY OF PEDIATRICS

THE meeting of the Executive Board was called to order at 10 A.M. Nov. 30, 1935, at the Georgian Hotel, Evanston, Ill., with Dr. Henry Dietrich, president, in the chair, all members being present.

It was decided to hold the next annual meeting at the President Hotel, Kansas City, Mo., on Monday, May 11, and Tuesday, May 12. The program will consist of two sets of twelve round-table discussions, each for thirty members; one session of two panel discussions and one session of business meeting with perhaps extra papers. It was decided that we would dispense with stenographers at the round-table discussions and try to have the meetings covered by means of secretaries designated from the membership. It was suggested that at the meeting of state chairmen Monday evening the problems of school medical inspection be discussed.

It was decided that beginning July 1, 1936, the dues should be raised to $20. This will enable us to balance our budget for the year 1936-1937.

The reports of the various committees were approved and the Committee on Clinical Investigation and Scientific Research was given a vote of thanks for its efforts.

The resignation of Dr. Bennett A. Melgaard of Sioux City, Iowa, was accepted.

The following men were elected to membership:

Region I

William B. Adams, Longmeadow, Mass.
Louis, Barash, New York, N. Y.
Ben Benjamin, Montreal, Que., Canada
Howard W. Brayton, Hartford, Conn.
Arthur W. Chapman, Glen Falls, N. Y.
F. H. Clark, Jamestown, N. Y.
Stewart H. Clifford, Boston, Mass.
R. Edward Corley, Burlington, Vt.
Thomas P. Cunningham, Worcester, Mass.
Bernard S. Denzer, New York, N. Y.
Louis K. Diamond, Boston, Mass.
Otto A. Faust, Albany, N. Y.
Hyman Peter Fine, Perth Amboy, N. J.
Carl C. Fischer, Philadelphia, Pa.
Jerome Glaser, Rochester, N. Y.
Edward S. Goodwin, Albany, N. Y.
Morris Greenberg, New York, N. Y.
Fairfax Hall, New Rochelle, N. Y.
Joseph L. Hetzel, Waterbury, Conn.
Eliot Hubbard, Jr., Cambridge, Mass.
Russell H. Iler, Brooklyn, N. Y.
Morris Ingall, Boston, Mass.
Harold Jacobziner, New York, N. Y.
Abel Lax, Montreal, Que., Canada
Lionel M. Lindsay, Montreal, Que., Canada
Harry L. F. Locke, Hartford, Conn.
Julian M. Lyon, Ardmore, Pa.
W. Frederick Mayer, Johnstown, Pa.
Rustin McIntosh, New York, N. Y.
Joseph C. Merriam, Farmingham, Mass.
Katharine K. Merritt, New York, N. Y.
Doris A. Murray, Rochester, N. Y.
Emanuel H. Nickman, Atlantic City, N. J.
David E. Overton, Hempstead, N. Y.
William Panitch, Newark, N. J.
John M. Parker, Rochester, N. Y.
Paul L. Parrish, Brooklyn, N. Y.
Joseph A. Ritter, Philadelphia, Pa.
Jacob Rosenblum, Brooklyn, N. Y.
Jacob L. Rosenstein, Jersey City, N. J.
Jacob L. Rothstein, New York, N. Y.
John P. Scott, Philadelphia, Pa.
George C. Sincerbeaux, Auburn, N. Y.
Carl H. Smith, New York, N. Y.
Mary B. Spahr, Ithaca, N. Y.
Jacob L. Stein, Brooklyn, N. Y.
Neil C. Stone, Poughkeepsie, N. Y.
John P. Stout, Jersey City, N. J.
Norman Survis, New Rochelle, N. Y.
Charles E. Wagner, Wilmington, Del.
Henry Washeim, Jr., Utica, N. Y.
Ruth H. Weaver, Philadelphia, Pa.
T. S. Wilder, Philadelphia, Pa.
Abbott L. Winograd, Nashua, N. H.
Henry P. Wright, Montreal, Que., Canada

Region II

Ruth G. Aleman, New Orleans, La.
J. H. Baumhauer, Mobile, Ala.
Mylnor W. Beach, Charleston, S. C.
B. J. Berger, Dallas, Texas
James R. Boulware, Jr., Lakeland, Fla.
Archbold M. Jones, Parkersburg, W. Va.

Howard J. Morrison, Savannah, Ga.
John M. Saunders, Nashville, Tenn.
Suzanne S. Schaefer, New Orleans, La.
A. Allen Shapero, Louisville, Ky.
John A. Shaw, Fayetteville, N. C.
J. B. Snow, Oklahoma City, Okla.
John B. Spencer, Gloucester, Va.

Region III

Clayton T. J. Dodge, E. Cleveland, O.
Paul D. Dwan, Minneapolis, Minn.
Harry M. Gilkey, Kansas City, Mo.
Richard C. Hiestand, Springfield, O.
Robert D. Hostetter, Dayton, O.
Thomas F. Humphrey, Xenia, O.
Ruth M. Mahon, Grand Forks, N. D.
Myrl M. Miller, Akron, O.
Samuel Okrent, Cincinnati, O.
John J. Pollack, Detroit, Mich.
William B. Raycraft, Oak Park, Ill.
Henry A. Sincock, Superior, Wis.
A. Leonard Van Horn, Columbus, O.
Damon O. Walthall, Kansas City, Mo.
James A. Wheeler, Newton, Kan.

Region IV

Arthur H. Gray, Seattle, Wash.
Harold C. Joesting, Butte, Montana
Douglas B. Leitch, Edmonton, Alta., Canada
Harold W. Price, Calgary, Alta., Canada
John M. Rector, San Francisco, Calif.
Alfred H. Spohn, Vancouver, B. C., Canada

On Sunday morning, December 1, at 10 A.M., the Executive Board met at the same location, with two representatives of the Committee on Allocation of Research Funds, Dr. Thomas B. Cooley and Dr. Fritz B. Talbot. After a thorough discussion of the situation, the Executive Board passed the following resolutions:

1. That the Committee on Allocation of Research Funds shall be reconstituted as the Council for Pediatric Research of the American Academy of Pediatrics.

2. That it would welcome the endorsement of this council by the American Pediatric Society.

3. That this council shall consist of five or more members.

4. That one member and not more than one each year shall retire.

   a. That retiring age of each member shall be not greater than seventy years.

   b. Any retiring member is eligible to reelection.

5. That any retiring member shall be replaced by a member elected by the Executive Board of the American Academy of Pediatrics from two or more nominations of the council.

6. That it is the sense of the Executive Board that as soon as possible the council shall be organized as an autonomous unit within the Academy.

REPORT OF THE COMMITTEE ON CLINICAL INVESTIGATION AND SCIENTIFIC RESEARCH OF THE AMERICAN ACADEMY OF PEDIATRICS, 1935

YOUR committee has received the request of the American Academy of Pediatrics that it investigate and report "on the subject of the monopolistic control of sources of the antirachitic vitamin D other than cod liver oil by the Wisconsin Alumni Research Foundation, to which the Steenbock patent for the activation of the ergosterol in foodstuffs by irradiation was assigned." Attention was drawn to this subject by a letter addressed to the Academy of Pediatrics.

It was stated that the price of viosterol was excessive; that instead of safeguarding the public as was their declared reason for the patenting and monopoly of the process of activating ergosterol as such or in foods, they appear to have maintained throughout a purely commercial attitude of exploiting the patent rights to the maximum extent for gain; that the Foundation has failed to safeguard the public against the possible dangers of multiple sources of the potent product vitamin D and has imposed conditions which make the price of the vitamin, either in viosterol or in milk vitaminized by feeding irradiated yeast to cows, an exorbitant figure.

As a preamble to discussion of specific points at issue, the Committee has thought it advisable to formulate some statement of present medical opinion regarding vitamin D, using that term in the broad sense, to cover all antirachitic agents.

1. Vitamin D is of proved value in the prevention and treatment of rickets, tetany, and osteomalacia. While there is evidence of a probable value in other conditions, these are not yet well defined, and the evidence has not had general acceptance.

2. Under present conditions of American life, it is *essential* that vitamin D be supplied throughout the period of infancy. It is *important* that it be continued throughout the period of transition to a general mixed diet. After this time clear-cut indications for its use are seldom met with, with the possible exception of adolescence, and the more certain exception of pregnancy and lactation. These are discussed below.

3. There is some evidence that during the adolescent period additional vitamin D may forestall some demineralization of bone and teeth of a type similar to that observed in osteomalacia, while during pregnancy and lactation such fortification of the diet is probably advisable, in order to prevent osteomalacia, and to increase the calcium and phosphorus content of the milk.

4. It is an unfortunate fact that our only present method of measuring the vitamin D potency of foods and drugs is in terms of rat units, for it is well known to investigators that D-containing substances of equal rat unitage but prepared by different means vary so widely in their effect on humans that they cannot be satisfactorily compared by any present standard. This injects an element of great uncertainty into any discussion of relative D-values of such substances as cod liver oil, viosterol, and the irradiated milks.

Your committee has conferred with representatives of the Foundation, and two of its number visited the offices of the Foundation in Madison, Wis. The committee were met by the Foundation and its representatives with the greatest courtesy, and all information requested was put at its disposal. A meeting was also held with licensees of the Foundation in New York last spring. As a result of the discussion which took place at this meeting, it was decided to request the Foundation to send a statement of its policies to the committee.

Your committee wishes first to state that it does not question the honesty of purpose of the trustees of the Foundation. It feels that the differences which have arisen in the point of view of the trustees and that of the medical profession could have been prevented if proper emphasis had been given to the safeguarding of the general public when the purposes and policies of the Foundation were first established.

The Foundation was organized on November 14, 1925. Its purpose is to "promote, encourage, and aid scientific investigations and research at the University and to assist in providing the means and machinery by which the scientific discoveries and inventions of the staff may be developed and patented and the public and commercial uses thereof determined; and by which such utilization may be made of such discoveries and inventions and patent rights as may tend to stimulate and promote and provide funds for further scientific investigation and research within said University."

Each patent has to pay for itself and all expenses incurred. If, then, there is any return from the patent, this return goes 15 per cent to the inventor and 85 per cent to the Foundation. This contract compared with other university foundations is very favorable to the Foundation. Lehigh University and Iowa State University give 50 per cent to patentee and 50 per cent to the Institute of Research. California Institute of Technology gives about 75 per cent to the inventor. Doctor Steenbock turned over his patent to the Wisconsin Alumni Foundation "lock, stock and barrel," without any strings tied to it. When the Wisconsin Alumni Foundation finally worked out its agreement with patentees and the income was divided on the above basis, Doctor Steenbock returned the first check representing 15 per cent of the proceeds of his patent. It was only after Doctor Steenbock was made to realize that all patentees in the Foundation should be on the same basis was he willing to accept his royalty.

The personnel of the trustees is as follows: George I. Haight, Chicago; W. S. Kies, New York; Judge Evan A. Evans, Chicago; L. M. Hanks, Madison; T. E. Brittingham, Jr., Madison; and Timothy Brown, Madison. July 1, 1930, H. L. Russell was elected director of the Foundation in which capacity he assumed the executive management of the work of the Foundation. Doctor Russell was for many years professor of bacteriology of the University of Wisconsin. Later he was dean of the agricultural school up to the time when he was summoned to the directorship of the Foundation.

The trustees early adopted the two following policies:

1. To build an endowment principal of substantial amount, the annual income of which might be used to advance research in the University.

2. To accumulate a reserve that is necessary to protect the inventions at stake.

The importance of the latter is seen by the fact that there are fourteen cases pending at the present time concerning infringements et cetera.

It is of interest to know that the first money that came to the Foundation was supplied by the trustees themselves and the first payment under the Steenbock patent was from the Quaker Oats Company which was worried about its product as Mellenby's work apparently showed that oatmeal was rickets producing. They were, therefore, very much interested in the possibility of irradiating their product so that this would not be the case. Low vitamin potency of the cereal was indicated because of the supposed danger of hypervitaminosis at that time.

With regard to its relationship to the University of Wisconsin, the trustees have adopted the policy that all of its aids to research will be made through the regular University machinery for such purposes and not directly from the Foundation to any individual or department. After the requests for grants-in-aid have been approved by the Foundation trustees, the lists of projects and accompanying grants are submitted through the dean of the Graduate School and the president of the

University to the Board of Regents of the University for their consideration. If approved and accepted by them as meeting the University policy with reference to gifts, the Foundation treasurer then transfers to the secretary of the University the requisite moneys, the secretary setting up the necessary credits on his books for the respective projects, all requisitions and expenditures. In this way the University officials retain full and complete control of the nature of the project studied, appointment of all staff members working on the same, all expenditures made, and a complete disposition of results as to mode of publication or otherwise. At the present time, the Foundation is supporting 100 different projects. These funds are divided into three groups: (1) grants-in-aid, (2) professors on research leave, and (3) alumni research fellowships.

With regard to the price of viosterol, the royalty consists of 10 per cent of the wholesale price in the sale of viosterol and 5 per cent in the case of viosterol added to cod liver oil, depending upon the potency of the material added. On three occasions, in June, 1931, in September, 1933, and in September, 1934, the price of viosterol has been reduced about 24 per cent at the request of the Foundation. The royalty on a 5 c.c. bottle of 250-D viosterol, retailing at from 69 cents to 75 cents, is 3½ cents.

There are five licensees for the manufacture of viosterol: Parke, Davis & Company, E. R. Squibb & Sons, Mead Johnson & Co., Abbott Laboratories, and Winthrop Chemical Company, Inc. In the same retail store there are definite variations in the price of these products made under the same patent by the different manufacturers. There are three companies—the Cherry Burrell (Double Bubble), Hanovia Chemical Company, and the Creamery Package Company—which make machines for the irradiation of milk. The Hanovia Company now make a machine at the cost of $900 which is applicable to as small a production as 200 quarts a day at which a profit can be made in selling the milk at 1 cent per quart extra each day. The Foundation has made an effort to introduce irradiated milk without an increase in the price, but on account of the state laws and NRA it is impossible to add the antirachitic quality of the milk without an increase in price. There have been two machines put on the market, one by a Canadian company and the other by Kaestner, of Baltimore, which so far have not been licensed. The Foundation has no financial interest whatsoever in any company and derives no revenue from the sale of machines. Its profits are solely derived from the use of the process.

The Institute has two monthly service charges—one of $60.00 for the small dairies and one of $100.00 for the large dairies. The service charge consists of biologic assay which costs from $30 to $50 depending upon where it is done, service of controlled advertising, and a medical and plant contact service. A copy of a contract shows that the royalty on irradiation of milk varies from $\frac{1}{10}$ to $\frac{1}{50}$ of a cent per quart. Up to the present time the total income from the service charge as well as the royalty does not equal the amount of money that has been put into the development of the process by the Foundation. The cost of the process of the irradiation of milk for a small dairy putting out from 200 to 300 quarts a day is from ½ to $\frac{2}{3}$ of a cent per quart; for the large dairies, ⅓ of a cent per quart, so that at the increased price of 1 cent it should be possible for them to make an additional profit. It should be remembered that it was the intention of the Foundation to have milk irradiated at no extra cost to the consumer, and it was so introduced in a number of places where, however, because of the objection of other dairymen and state laws, it was impossible to sell it at the same price as the same grade of ordinary milk.

There is no pressure brought to bear upon the manufacturers of viosterol against the distribution of viosterol for its use in milk. It is, however, the inability to control the antirachitic factor when it is added in this way that has made the Founda-

tion refuse to license the production of vitamin D milk in this manner. The contract with the Borden Company is no different from the contract with any other company. The Fleishmann Yeast Company now produces a 70-D yeast. In order to have two sources of irradiated ergosterol the Foundation has licensed the irradiation of yeast by the Fleishmann Company and the irradiation of molds produced by the Acetol Products Company—a DuPont company. These two companies pay the Foundation a flat yearly rate. The product of the Acetol Company is used by the Toronto Foundation in the production of vitamin D bread. These companies make the irradiated products and can sell only to milk producers who are licensed under the Wisconsin Alumni Foundation. This makes possible a double check, one on the amount of yeast purchased and one on the antirachitic properties of the milk by biologic assay. Viosterol can be bought to be put into milk but this process will not be licensed by the Wisconsin Foundation because they do not feel it can be adequately controlled. The irradiated dried yeast is sold to the farmer at 27 cents a pound, which increases the cost of milk about ½ cent per quart. The Foundation receives $1 per cow per year fed the irradiated yeast, and a royalty of 2 cents a pound on dried yeast fed in this way, no inconsiderable part of which is used in determination of standards of vitamin content.

In the first report of the Foundation the amounts allotted for research were given.

Table I gives the various products now being licensed at the present time:

1. Pharmaceuticals, viosterol and fortified cod liver oil.
2. Foods.

TABLE I

VITAMIN D FOOD PRODUCTS (NOT INCLUDING PHARMACEUTICALS AND CERTAIN MALT PRODUCTS) LICENSED BY THE WISCONSIN ALUMNI RESEARCH FOUNDATION

PRODUCT	MANUFACTURER	POTENCY (INT. UNITS)	DATE LICENSED
Rolled Oats	Quaker Oats Co. Chicago, Ill.	3 to 5 units per ounce	1927
Muffets		3 to 5 units per ounce	1927
Farina		Originally: 3 to 5 units per oz. Now: 1,000 units per oz.	1927
Foil Yeast	Standard Brands, Inc. New York City	160 units per cake	1928
Dry Yeast		2,700 per gram.	1928
Sunwheat Biscuit	McCormick Mfg. Co. London, Ontario	20 units per ounce	1929
Bond Bread	General Baking Co. New York City	255 units per loaf	1929
Hygeia Vegetables	Hygeia Nursing Bottle Co. Buffalo, N. Y.	----------	1931 discontinued
Snider's Tomato Juice	Snider Packing Co. Rochester, N. Y.	No data available	1931 discontinued
Bio-Vegetin	Bio-Vegetin Prod. Co. Chicago, Ill.	No data available	1931 discontinued
Sunfed Flour	Sunfed Flour Mills, Minneapolis, Minn.	380 units per pound	1933
Dryco	Dry Milk Co. Bainbridge, N. Y.	35-40 units per ounce	1931
Irradiated fluid milk	135-140 licensees	135 units per quart	1933
Irradiated evaporated milk	5 licensees	135 units per quart (1:1 dilution)	1934
Metabolized "D" milk (Yeast fed to cows)	220-225 licensees	430 units per quart	1932
Cocomalt	R. B. Davis Co. Hoboken, N. J.	80 units per ounce (dry)	1931

Other malt products licensed, which are almost in the pharmaceutical class, include A. B. D., Irradol Malt, Irradol Malt A, Haliver Malt, and Neochemical Food.

The Foundation has had numerous requests from oleomargarine companies, tobacco companies, candy companies, and various other food companies but has refused to grant licenses for use in such products.

With regard to guarding the public against multiple sources of vitamin intake, it has been very definitely shown that hypervitaminosis in such doses as used in food products does not occur. Harmful doses have been kept constantly in mind and only recently has the Foundation allowed the addition of ergosterol or yeast to increase the vitamin content of certain foods. The Foundation feels that bread, cereals and milk are the food products that should be fortified by vitamin D. With regard to criticism, the American Medical Association has criticized the Foundation because they have not been active enough in the development of vitamin milk. On the other hand, there has been a great deal of criticism from other sources because they have been too active. Former criticisms were that they were withholding something that was of benefit to the public and that they were doing something for profit rather than the good of the public. There have been numerous attempts made to dilute viosterol with oil and bootleg it at a lower price. The Foundation has used legal measures to prevent this wherever it has been found. This is given as another reason why the size of the package of viosterol has been kept so small.

The advertising of irradiated products is controlled by the Foundation. All advertisements recommended by the Foundation are first approved by the American Medical Association Committee on Foods. Such advertisements usually possess some educational value for the public.

It is evident also that there is no ground for animus against the directors of the Wisconsin Foundation, who are unquestionably endeavoring to the best of their ability to carry out an altruistic purpose in utilizing for the purpose of scientific research the profits derived from an important medical discovery. It is their misfortune, perhaps, that these profits have been so great as to make them the target for criticism, much of which belongs rather to a system of which they are the most conspicuous representatives. No one would think of classing them with the holders of a patent which is used deliberately to suppress rather than to further research.

The committee believes the economic costs to the public of the products licensed under the Foundation are of equal importance to their scientific value. Perhaps the relative importance of these two factors has been considered and balanced by the trustees of the Foundation, but as events have shown the cost to the public has been in the opinion of the committee unnecessarily high. The committee, however, is not in the position to determine from the information at hand what constitutes a fair profit. Table I shows the items of which the costs to the public are made up. It seems to us that some method might be developed to place this valuable therapeutic agent in the hands of the public at a lower price by increasing the efficiency of distribution and eliminating some of the profits listed in Table I under advertising, selling, administration, druggist's and manufacturer's profits—more particularly that of the retail druggist.

Table II illustrates the cost of viosterol on the market obtained by the committee. Although it is clear from the table that a reduction in the royalty paid to the Wisconsin Alumni Foundation would only reduce the retail cost an insignificant amount, there are other items which go to make up the cost to the public which appear out of proportion.

The Wisconsin Alumni Foundation in following out its purpose of contributing to and aiding research says very frankly that it has been able to aid the University of Wisconsin very materially during the trying years of the depression. Because of this and because of what they believe to be a high cost of the product to the com-

TABLE II

ITEMIZED COST OF MINIMUM UNIT OF VIOSTEROL*
(5 C.C. PACKAGE 250-D)

Cost of viosterol itself	0.7 cents	
Packing supplies and labor	3.4 cents	
Factory overhead	0.9 cents	
Total cost of manufacturing		5.0 cents
Factory research and laboratory control (assays)	3.7 cents	
Research fellowship grants	5.1 cents	
Total cost of developing		8.8 cents
Advertising, selling, administrative expense		11.0 cents
Manufacturer's net profit		7.6 cents
Royalty to Wisconsin Foundation		3.6 cents
Wholesale druggist's gross profit		6.0 cents
Retail druggist's gross profit		23.0 cents†
Selling price (total)		65.0 cents

*These figures represent an average of several manufacturers.

†The retail druggist is at liberty to cut his profit and reduce the price. The minimum code price is 43 cents. Prices below 60 cents are common in large cities. Prices below 50 cents are rare.

munity, the trustees, in the opinion of many members of the medical profession, are not following the purposes of the Trust to protect the public from exploitation.

The considerations mentioned above made it clear to the committee that the problem was not one concerning the Wisconsin Alumni Foundation alone, but was of a much wider scope than was originally supposed. Back of it all were problems in which debatable general principles were involved.

It centers about the desirability of university patents, especially in their relation to public health and medicine. "This matter of patenting scientific discoveries is an involved question that has many sides. Scientific men differ among themselves in regard to ethics and wisdom of this procedure." There are, in general, two main points of view, the one admirably expressed in an address before the American Physiology Society in 1934, by Dr. William H. Howell, who believes that discoveries in medicine or science which alleviate human suffering or promote in any way the welfare of humanity should belong to the public and their benefits be freely enjoyed by all without any pecuniary profits. The other, which the Wisconsin Alumni Foundation exemplifies, is that of patenting such discoveries "where a lack of proper control in the use of the patented article or method might result in undue exploitation of the public, in lack of uniformity in standardization, and in confusion of the public mind as to the inherent values of the product. The Foundation feels that it is justified in receiving reasonable royalties upon certain types of medical discoveries for the reason that such royalties over and above the necessary costs of control are entirely devoted to scientific research from which research the public receives or may receive direct benefit in further new discoveries and developments."

There are two distinct schools of university thought, the one which rules that discoveries which are made "through members of its faculties or otherwise, which result, in the field of medicine, in the alleviation of human suffering or in the field of science, in promoting in any way the welfare of humanity, should not be restricted by the university, but should be announced to the world so that such benefits may be fully enjoyed by all, and without pecuniary profits either to the university or to any one in its service."

The other is exemplified by the Wisconsin Alumni Foundation, which, although organized independently of the University of Wisconsin, contributes largely to that university. The following quotation illustrates this: "The depression this country has recently passed through has made it necessary for the Foundation to come to the aid of the University in the maintenance of the latter's research program to the extent that during the University biennium 1933-1935 the Foundation carried a substantial part of the financial burden of the entire University's research program, a sum aggregating $319,176."

This sum of money was used by the Alumni Foundation for "furtherance of scientific research at the University of Wisconsin." In other words, the public as a whole is taxed for the benefit of an institution. This philosophy is not confined to the Wisconsin Alumni Foundation alone and is seen in the policies of many other universities.

Unfortunately the picture has been obscured by grouping all types of patents under one heading and will not be completely thought out until patents having to do with public health and medicine are considered separately.

The whole question is being studied by two committees, one representing the American Association for the Advancement of Science, and the other the National Research Council. The latter has announced as its policy patenting discoveries made under its grants and dedicating its patents to the public. Your committee feels that it would be an unnecessary and costly reduplication of work for them to enter into this field of inquiry and is therefore not prepared to express an opinion as to how the patent situation should be handled. It is convinced that all patents cannot be treated in the same manner and that there should be a sharp distinction between patents which deal with public health and medicine and those which have no direct bearing on them. Knowledge of the whole patent situation will be necessary before a clear picture is possible. It recommends, therefore, that no action be taken until the National Research Council and the American Association for the Advancement of Science conclude their investigations and take action. Until this is done, it will not be possible to make any recommendation in regard to the Wisconsin Alumni Foundation other than to urge that every effort be made to reduce the price of their products to the public.

Respectfully submitted,

FRITZ B. TALBOT, M.D.
JOSEPH BRENNEMANN, M.D.
HENRY F. HELMHOLZ, M.D.

Academy News

Dr. Matthew Winters of Indianapolis has been appointed chairman for Indiana, to replace Dr. Torian, who resigned.

Dr. Harold C. Joesting, Butte, has accepted the chairmanship for Montana.

News and Notes

The following men have been certified by the American Board of Pediatrics since the last report.

Dr. George B. Bader, New York, N. Y.
Dr. Elmer Walter Barron, Boston, Mass.
Dr. Tobias L. Birnberg, St. Paul, Minn.
Dr. Robert E. Cummings, Chicago, Ill.
Dr. Clarence F. Friedman, Brooklyn, N. Y.
Dr. Joseph Garland, Boston, Mass.
Dr. Howard B. Hamilton, Omaha, Neb.
Dr. Alfred Collard Henderson, Stamford, Conn.
Dr. Jerome L. Kohn, New York, N. Y.
Dr. Robert H. Kotte, Cincinnati, Ohio
Dr. Julian M. Lyon, Ardmore, Pa.
Dr. Herman L. Maslow, Brooklyn, N. Y.
Dr. W. Ambrose McGee, Richmond, Va.
Dr. A. Lane Mitchell, Houston, Texas
Dr. Arthur Gardner Quinn, Memphis, Tenn.
Dr. John Porter Scott, Philadelphia, Pa.
Dr. Norman Survis, New Rochelle, N. Y.
Dr. Donald Kendrick Woods, San Diego, Calif.
Dr. Harry S. Andrews, Louisville, Ky.
Dr. George Lamar Arrington, Meridian, Miss.
Dr. James Lewis Blanton, Fairmont, W. Va.
Dr. Harry H. Boyle, Chicago, Ill.
Dr. James Bennett Gillespie, Urbana, Ill.
Dr. David William Goltman, Memphis, Tenn.
Dr. Edgar Alphonso Hines, Seneca, S. C.
Dr. Cecil Oliver Lorio, Baton Rouge, La.
Dr. Robert H. McCrackin, Elat, Africa
Dr. James Dallas McKinney, Champaign, Ill.
Dr. John Collins McKitterick, Burlington, Iowa
Dr. Herman Frederic Meyer, Chicago, Ill.
Dr. Ben H. Nicholson, Oklahoma City, Okla.
Dr. Lee Palmer, Louisville, Ky.
Dr. Harold D. Pyle, South Bend, Ind.
Dr. Warren Wilson Quillian, Coral Gables, Fla.
Dr. Heyworth Naylor Sanford, Chicago, Ill.
Dr. Mary Burchard Spahr, Ithaca, N. Y.
Dr. Brick Pomeroy Storts, Tucson, Ariz.
Dr. Ernest Starr Watson, Elmhurst, Ill.
Dr. Walter Merrill Whitaker, Quincy, Ill.
Dr. Robert E. Williams, Chicago, Ill.
Dr. Robert Ermon Wilson, Greenville, Miss.
Dr. Max Reagan Woodward, Sherman, Texas
Dr. Meldrum Keplinger Wylder, Albuquerque, N. M.

In this group twenty-five were certified on examination. At the examination held in St. Louis, on November 19 and 20, 1935, thirty-one men took the examination and six failed. Of the twenty-five who passed, four were in Group I, seven in Group II, and fourteen in Group III. Of the men who failed, one was in Group II, and five were in Group III.

The following should be added to the list of House Officer Positions in Pediatrics, Vol. 7, p. 427, 1935 (see pp. 427 and 428 for key).

New York, N. Y.	**A**	**B**	**C**	**D**
Bellevue—Charles H. Smith, New York University	3	4	4	

C75 B110 NB80 P A2039 D196-138 OPD 1/1 7/1
A 3 $75 *abd* OPD W B4 NS *abc* OPD W C4 *ab* NS OPD W

Dr. Joseph I. Linde, clinical professor of pediatrics in the Yale University School of Medicine, has been appointed health officer of New Haven. This is the position formerly held by Dr. John L. Rice, now health commissioner of New York City. Dr. Linde has had a long and distinguished record in pediatrics and public health work in New Haven and in Connecticut. At the present time he is chairman of the Committee on Public Health, State Medical Society; chairman for Connecticut, American Academy of Pediatrics; chairman of Health Division of the Council of Social Agencies and member of the executive committee; medical director, Child Welfare Conferences of the Visiting Nurses' Association; past president, New Haven County Medical Society.

A meeting of the **Hezekiah Beardsley Pediatric Club of Connecticut** was held at Seaside, the state sanatorium for bone and gland tuberculosis, Waterford, Conn., Nov. 14, 1935.

Following an inspection of the plant, which is beautifully situated on the north shore of Long Island Sound near New London, the following program was presented:

Discussion of the proposed state health program, led by Dr. A. Elizabeth Ingraham, director of the Department of Child Hygiene, Connecticut State Department of Health; and open discussion on the following subjects:

"Measles Prophylaxis With Placental Extract," "Use of Fatty Acid Unsaturates in the Treatment of Infantile Eczema."

The following officers were elected for the coming year: Dr. Howard W. Brayton, Hartford, president; Dr. Ernest Caulfield, Hartford, secretary; and Dr. Edward T. Wakeman, New Haven, treasurer.

Following the meeting, dinner for the Society was provided by the Institution.

The Hospital of St. Raphael, of New Haven, is about to open a new children's pavilion. The new unit, separate from the general hospital but adjoining, will accommodate about forty infants and children and is modern in every detail.

The **American Board of Pediatrics** wishes to call the attention of all pediatricians to the fact that after September, 1936, no man with ten years' experience or more will be certified without examination.

The next examination by the **American Board of Pediatrics** will be held on May 9, in Kansas City, Mo., preceding the meetings of the American Academy of Pediatrics and the American Medical Association.

Dr. William Perry Northrup died Nov. 20, 1935, in New York. Dr. Northrup was professor of pediatrics at New York University and Bellevue Hospital Medical College from 1893 to 1920. Since 1920 he had been emeritus professor of pediatrics at New York University. At one time he taught Greek at Knox College, Galesburg, Ill. He was attending physician at the Presbyterian Hospital.

He was a member of many medical societies and served as president of the New York Pathological Society, the American Pediatric Society in 1899, and the Association of American Physicians. He was associated with Dr. O'Dwyer in the development of intubation for the treatment of laryngeal diphtheria. He was also interested in the treatment of acute infectious diseases, particularly pneumonia, by cold, flowing fresh air and originated the first open-air hospital ward.

Book Review

Growth: A Study of Johnny and Jimmy. MYRTLE B. MCGRAW, New York, 1935, D. Appleton-Century Company.

To review this study of the behavior of infants in a few words is difficult because of the large amount of closely packed information given. The experiment, to study the growth and development of behavior in identical twins one of whom was subjected to much training while the other was restricted in his activities, was well conceived by the author. The fact that the experimental babies turned out to be fraternal instead of identical twins interfered considerably with the value of the comparative observations but does not detract from the observations the author has made in outlining the course of developing behavior patterns—to my mind the outstanding contribution of the book.

The author conceives of behavior as a growing technic of the baby, and she records the details of growth of each ability studied during the entire observable period. This method of observation is presented in contradistinction to the "cross-section" method in which accomplishments are merely noted at the age levels at which they emerge as attainments. Obviously this type of study opens a wide field for investigation of the question as to *why* babies behave as they do rather than *when* they so react.

In studying phylogenic activities she details her observations on both twins as to the Moro reflex, the grasping reflex, crawling, creeping, walking, sitting and other postural achievements, reaching and prehensile activities, and reactions to cutaneous irritation. Comparative results on the practiced and unpracticed babies seem to show that in the main, these predominantly infracortically controlled acts are very slightly influenced by practice. The various steps in the growth of the abilities showed up at approximately the same time in both infants. However, practice did alter the baby's attitude toward the activity and to a certain extent improve the quality of the attainment. Thus, "while the use of the activity will not advance appreciably the day a child begins to walk alone and will not alter the general method of progression, exercise may influence the grace with which he steps, his speed, and his mien of progression."

Many of these behavior patterns begin at an infracortical level and later on are supplanted by similar activities cortically controlled. Her evidence seems to show that the longer the time elapsed in this infracortical to cortical control period, the greater are the possibilities for modification by exercise.

Predominantly ontogenetic activities were then studied, such as swimming, diving, climbing, descending, skating, jumping, and manipulation of heavy objects. The growth course of such behavioral achievements was recorded. It was apparent that such performances were much more subject to modification by practice than were those of phylogenic origin.

From these simpler activities she turns to a study of the development of associational activities, retention and recall, language, understanding of relations, and anticipatory reactions. An outstanding contribution of this experiment is the demonstration that the time at which education is attempted is a consideration fully as important as the educational technic. The optimal time to apply education is, she thinks, "when a new aspect of the behavior pattern arises, before it has attained definition." Duration of effort was also found to be important. Even in

the higher, more complex activities, however, it was found that by later training the twin who was held back, Jimmy, could be brought to approximately the same performance as the practiced one, Johnny.

Exercise in many fields did not seem to benefit remarkably in a new project, as both twins ultimately reached approximately the same ability in solving more complicated situations which were devised. Johnny, the practiced one, however, seemed to have attained a better attitude toward problems than had Jimmy.

The work, well thought out and painstakingly done, is well worth the careful attention of any one dealing with the problems of child behavior. Emphasis on the time when our efforts should be expended is particularly important. We have thought much about technics of education and little about chronologic factors. The concept that behavior develops according to rules of growth is sound, and the author's tracing of these patterns from their earliest discernible beginnings to maturation makes a fascinating study.

C. A. A.